Official Protocol Title:	A Phase 3, Randomized, Double-blind Trial of Pembrolizumab (MK-3475) Plus Enzalutamide Plus ADT Versus Placebo Plus Enzalutamide Plus ADT in Participants With Metastatic Hormone-Sensitive Prostate Cancer (mHSPC) (KEYNOTE-991)
NCT number:	NCT04191096
Document Date:	15-May-2023

Title Page

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Protocol Title: A Phase 3, Randomized, Double-blind Trial of Pembrolizumab (MK-3475) Plus Enzalutamide Plus ADT Versus Placebo Plus Enzalutamide Plus ADT in Participants With Metastatic Hormone-Sensitive Prostate Cancer (mHSPC) (KEYNOTE-991)

Protocol Number: 991-04

Compound Number: MK-3475

Sponsor Name: Merck Sharp & Dohme LLC (hereafter called the Sponsor or MSD)

Legal Registered Address:

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IND	122753

Approval Date: 15 May 2023

Sponsor Signatory

Typed Name: Date
Title:

Protocol-specific Sponsor contact information can be found in the Investigator Study File Binder (or equivalent).

Investigator Signatory

I agree to conduct this clinical study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol.

Typed Name: Date
Title:

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 04	15-MAY-2023	Protocol amended consistent with recommendations of the eDMC after an interim review of the data; specifically, to discontinue the study due to futility.
Amendment 03	07-OCT-2022	Sponsor underwent an entity name change and update to the address.
Amendment 02	14-MAY-2021	To update the dose modification and toxicity management guidelines for irAEs.
Amendment 01	09-FEB-2021	To add an extension portion in China to allow for the required exposure and number of events to investigate efficacy and safety in participants enrolled in China.
Original Protocol	31-OCT-2019	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 04

Overall Rationale for the Amendments:

Protocol amended consistent with recommendations of the eDMC after an interim review of the data; specifically, to discontinue the study due to futility.

Summary of Changes Table:

Primary Reason for Amendment		
Section # and Name	**Description of Change**	**Brief Rationale**
1.1 Synopsis	Statements added to describe the safety and efficacy results of the IA leading to the determination of futility.	This change was made to address recommendations of the eDMC after interim review of data.

Other Reasons for Amendment		
Section # and Name	**Description of Change**	**Brief Rationale**
Throughout Document	The structure of the protocol has been updated.	To comply with current industry regulations and guidelines. This restructuring does not affect the clinical or regulatory integrity of the protocol. All other relevant changes and their primary reasons are included for completeness.
1.1 Synopsis, Estimated Duration of Study	The estimated duration of the study has been changed.	See rationale for 1.1.
1.1 Synopsis, Study Governance Committees	Executive Oversight Committee and eDMC are no longer applicable.	See rationale for 1.1.
1.1 Synopsis, Hypotheses, Objectives, and Endpoints	Participants on study treatment will have local tumor imaging assessments per SOC. Central tumor response, ePRO, SSRE, PSA assessments will no longer be performed; CCI [redacted] will no longer be collected.	See rationale for 1.1.
1.3 Initial Treatment Phase (Pembrolizumab/Placebo Plus Enzalutamide Plus ADT)	Participants on study treatment will have local tumor imaging assessments per SOC. Central tumor response, ePRO, SSRE, PSA assessments will no longer be performed; CCI [redacted] will no longer be collected.	See rationale for 1.1.

Other Reasons for Amendment		
Section # and Name	**Description of Change**	**Brief Rationale**
2.3 Benefit/Risk Assessment	Analyses of safety endpoints will be performed at the end of the study. No further analyses of efficacy and ePRO endpoints will occur after IA1 cutoff date.	See rationale for 1.1.
3 Hypotheses, Objectives, and Endpoints	Participants on study treatment will have local tumor imaging assessments per SOC. Central tumor response, ePRO, SSRE, PSA assessments will no longer be performed; CCI [redacted] will no longer be collected.	See rationale for 1.1.
4.1 Overall Design	Added note describing actions taken with study intervention and specify which analyses and procedures will not continue to be performed.	See rationale for 1.1.
4.2.1.3 Patient-reported Outcomes	ePRO assessments will be discontinued.	See rationale for 1.1.
4.4.1 Clinical Criteria for Early Study Termination	Safety and efficacy analysis results of the IA noted.	See rationale for 1.1.
6.1 Study Intervention(s) Administered	All study participants should stop ongoing treatment with pembrolizumab/placebo, unless benefitting and approved by Sponsor to continue the combination. All other study participants should be discontinued from study and be offered SOC.	See rationale for 1.1.
6.3.3 Blinding	Study unblinded due to result of IA1.	See rationale for 1.1.
6.6.3 Immune-Related Events and Dose Modification (Withhold, Treat, Discontinue)	Updated hypothyroidism and myocarditis sections of Table 7.	Alignment with the current dose modification guidelines.
7.1 Discontinuation of Study Intervention	Central tumor response assessments will be discontinued and performed locally per SOC in participants on study treatment.	See rationale for 1.1.
8.1.10 Participant Blinding/Unblinding	Study unblinded due to result of IA1.	See rationale for 1.1.
8.2.1 Tumor Imaging and Assessment of Disease	Central tumor response assessments will be discontinued, and local tumor imaging should continue per SOC schedule.	See rationale for 1.1.

Other Reasons for Amendment		
Section # and Name	**Description of Change**	**Brief Rationale**
8.2.1.5 Symptomatic Skeletal-Related Events	SSRE assessments will be discontinued.	See rationale for 1.1.
8.2.2 Prostate-specific Antigen Assessments	PSA assessments will be discontinued.	See rationale for 1.1.
8.2.4 Patient-reported Outcomes	ePRO assessments will be discontinued.	See rationale for 1.1.
CCI [redacted]		
8.10.2.3 Second Course	Second Course has been discontinued.	See rationale for 1.1.
8.10.3.2 Follow-up Visits	Follow-up visits will be discontinued.	See rationale for 1.1.
8.10.3.3 Survival Follow-up	Survival Follow-up visits will be discontinued.	See rationale for 1.1.
9 Statistical Analysis Plan	Clarifying analyses to be performed.	See rationale for 1.1.
9.1 Statistical Analysis Plan Summary	Clarifying analyses to be performed.	See rationale for 1.1.
9.6 Statistical Methods	Clarifying analyses to be performed.	See rationale for 1.1.
9.7 Interim Analyses	Clarifying analyses to be performed.	See rationale for 1.1.
9.7.2 Safety Interim Analyses	Clarifying analyses to be performed.	See rationale for 1.1.
9.8 Multiplicity	Clarifying analyses to be performed.	See rationale for 1.1.
9.9 Sample Size and Power Calculations	Clarifying analyses to be performed.	See rationale for 1.1.

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[redacted]

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 3, Randomized, Double-blind Trial of Pembrolizumab (MK-3475) Plus Enzalutamide Plus ADT Versus Placebo Plus Enzalutamide Plus ADT in Participants With Metastatic Hormone-Sensitive Prostate Cancer (mHSPC) (KEYNOTE-991)

Short Title: Phase 3 Study of Pembrolizumab/Placebo plus Enzalutamide plus ADT in mHSPC

Acronym: N/A

Hypotheses, Objectives, and Endpoints:

Hypotheses are aligned with objectives in the Objectives and Endpoints table.

In participants with mHSPC:

NOTE: Based on the data from an interim safety and efficacy analysis for KEYNOTE-991 (data cutoff 31-OCT-2022), eDMC recommended stopping the study for futility because pembrolizumab in combination with enzalutamide and ADT did not demonstrate an improvement in OS or rPFS, the trial's dual primary endpoints, compared to placebo plus enzalutamide and ADT and appears unlikely to do so in a future analysis. Based upon these data and the recommendation of the eDMC, the study was unblinded (as of 19-JAN-2023). All the prespecified interim analyses after IA1 and final analysis of the study described in the SAP will not be performed. Safety analysis will be performed at the end of the study; there will be no further analyses for efficacy and ePRO endpoints collected from participants beyond the IA1 cutoff date.

NOTE: In alignment with the study update memo sent to Investigators on 25-JAN-2023, all study participants should stop ongoing treatment with pembrolizumab/placebo. Exceptions may be requested for study participants who, in the assessment of their study physician, are benefitting from the combination of enzalutamide and pembrolizumab, after consulting with the Sponsor. All other study participants should be discontinued from study and be offered SOC treatment as deemed necessary by the Investigator. If enzalutamide as SOC is not accessible off study to the participant, central sourcing may continue. As of Amendment 04, participants who are still on study treatment will no longer collect central PSA blood samples, SSRE assessments, ePRO assessments (FACT-P, EQ-5D-5L, BPI-SF), CCI [redacted] **) or tumor response assessments by BICR. However, local tumor imaging assessments should continue per SOC schedule. In addition, Follow-up and Survival Follow-up visits will no longer be conducted. Updated analyses are described in Section 9.**

Primary Objective	**Primary Endpoint**
To compare pembrolizumab plus enzalutamide plus ADT versus placebo plus enzalutamide plus ADT with respect to **rPFS** per PCWG-modified RECIST 1.1 as assessed by BICR where soft tissue will be assessed per RECIST 1.1 modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, and bone disease will be assessed per PCWG criteria. Hypothesis (H1): The combination of pembrolizumab plus enzalutamide plus ADT is superior to placebo plus enzalutamide plus ADT with respect to **rPFS** per PCWG-modified RECIST 1.1 as assessed by BICR.	**rPFS:** the time from randomization to radiographic progression or death due to any cause, whichever occurs first.
To compare pembrolizumab plus enzalutamide plus ADT versus placebo plus enzalutamide plus ADT with respect to **OS.** Hypothesis (H2): The combination of pembrolizumab plus enzalutamide plus ADT is superior to placebo plus enzalutamide plus ADT with respect to **OS.**	OS: the time from randomization to death due to any cause.
Secondary Objectives	**Secondary Endpoints**
To compare pembrolizumab plus enzalutamide plus ADT versus placebo plus enzalutamide plus ADT with respect to **TFST**. Hypothesis (H3): The combination of pembrolizumab plus enzalutamide plus ADT is superior to placebo plus enzalutamide plus ADT with respect to **TFST**.	**TFST:** the time from randomization to initiation of the first subsequent anticancer therapy or death, whichever comes first.
To compare pembrolizumab plus enzalutamide plus ADT versus placebo plus enzalutamide plus ADT with respect to **TTSSRE**.	**TTSSRE:** the time from randomization to the first SSRE, defined as: • use of EBRT to prevent or relieve skeletal symptoms

Hypothesis (H4): The combination of pembrolizumab plus enzalutamide plus ADT is superior to placebo plus enzalutamide plus ADT with respect to **TTSSRE**.	• occurrence of new symptomatic pathologic bone fracture (vertebral or non-vertebral) • occurrence of spinal cord compression • or tumor-related orthopedic surgical intervention, whichever occurs first
To assess pembrolizumab plus enzalutamide plus ADT versus placebo plus enzalutamide plus ADT with respect to the: - **Time to PSA progression** - **Time to radiographic soft tissue progression** per soft tissue rules of PCWG-modified RECIST 1.1, as assessed by BICR - **TTPP** - **PFS2** as determined by investigator assessment	**Time to PSA progression:** the time from randomization to PSA progression. The PSA progression date is defined as the date of 1) ≥25% increase and ≥2 ng/mL above the nadir, confirmed by a second value ≥3 weeks later if there is PSA decline from baseline, or 2) ≥25% increase and ≥2 ng/mL increase from baseline beyond 12 weeks if there is no PSA decline from baseline. **Time to radiographic soft tissue progression:** the time from randomization to radiographic soft tissue progression. **TTPP:** time from randomization to pain progression based on BPI-SF Item #3 "worst pain in 24 hours" and opioid use. **PFS2:** time from randomization to disease progression as determined by investigator assessment of radiological or clinical progression after next-line of therapy or death from any cause, whichever occurs first.
To assess pembrolizumab plus enzalutamide plus ADT versus placebo plus enzalutamide plus ADT with respect to the: - **PSA response rate** - **PSA undetectable rate** - **ORR and DOR per PCWG-modified RECIST 1.1 as assessed by BICR**	**PSA response:** a PSA decline of ≥50% from baseline measured twice at least 3 weeks apart **PSA undetectable:** PSA <0.2 ng/mL during study intervention **OR: CR** or **PR** **DOR:** the time from the earliest date of the first documented evidence of CR or PR until earliest date of disease progression or death due to any cause, whichever occurs first
To assess the **safety and tolerability** of pembrolizumab plus enzalutamide plus ADT versus placebo plus enzalutamide plus ADT.	**AEs** Study intervention discontinuation due to AEs

Overall Design:

Study Phase	Phase 3
Primary Purpose	Treatment
Indication	Prostate cancer metastatic
Population	Participants with mHSPC
Study Type	Interventional
Intervention Model	Parallel This is a multi site study.
Type of Control	Placebo
Study Blinding	Double-blind with in-house blinding
Blinding Roles	Investigator Participant Sponsor
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 59 months from the time the first participant signs the informed consent until the last participant's last study-related telephone call or visit. Extension Portion in China: The Sponsor estimates that the study will require approximately 1 additional year (beyond the global study's last participant last study-related phone call or visit) from the time the first participant signs the informed consent until the last participant's last study-related telephone call or visit.

Number of Participants:

Global Portion: Approximately 1232 participants will be randomized as described in Section 9.1.

Extension Portion in China: Approximately 186 participants overall will be enrolled in China, including participants enrolled in either the global portion or the extension portion.

Intervention Groups and Duration:

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use
Arm 1	Pembrolizumab	25 mg/mL	200 mg	IV Infusion	Day 1 of each 21-day cycle	Test Product
Arm 1	Enzalutamide	40 mg/ 80 mg	160 mg	Oral	Four 40-mg capsules/ tablets orally per day/two 80 mg tablets orally per day	Test Product
Arm 2	Enzalutamide	40 mg/ 80 mg	160 mg	Oral	Four 40-mg capsules/ tablets orally per day/two 80 mg tablets orally per day	Test Product
Arm 2	Placebo	NA	NA	IV Infusion	Day 1 of each 21-day cycle	Placebo

Abbreviations: D Day; IV intravenous; NA not applicable; PO oral; Q3W every 3 weeks; QD once daily.

Total Number of Intervention Groups/Arms	2 arms
Duration of Participation	Each participant will participate in the study from the time the participant signs the Informed Consent Form (ICF) through the final protocol-specified contact. After a screening phase of up to 42 days, each participant will be assigned to receive study intervention (enzalutamide combination with either pembrolizumab or placebo) until disease progression is radiographically documented, verified by BICR per PCWG-modified RECIST 1.1, unacceptable AEs, intercurrent illness that prevents further administration of treatment, investigator's decision to discontinue the participant, or administrative reasons requiring cessation of treatment. All participants must maintain continuous androgen deprivation therapy (ADT) with a luteinizing-hormone releasing hormone (LHRH) agonist or antagonist during study treatment or have a history of bilateral orchiectomy. Treatment with pembrolizumab/placebo may continue for up to 35 cycles

	(approximately 2 years starting with the first infusion in Cycle 1) or until meeting criteria for discontinuation of study intervention. Treatment with enzalutamide will proceed continuously from Day 1 of Cycle 1 in both arms, unless criteria for discontinuation of study intervention are met (eg, disease progression). If pembrolizumab/placebo is completed or discontinued for reasons other than progressive disease, participants receiving enzalutamide will continue to receive enzalutamide and ADT (Extension First Course) until criteria for discontinuation are met (eg, disease progression). Participants who stop pembrolizumab as a result of obtaining an investigator-determined confirmed CR or those subjects who stop after receiving 35 cycles may be eligible for an additional 17 cycles of pembrolizumab (approximately 1 year) after progressive disease if they meet the criteria for re-treatment (Second Course Phase) and the study is ongoing (Section 8.10.2.3). Participants randomized to placebo will not be permitted to cross over to pembrolizumab following progression. After the end of treatment, each participant will be followed for the occurrence of adverse events and spontaneously reported pregnancy as described under Section 8.4. Participants who discontinue study treatment (pembrolizumab/placebo and enzalutamide) for reasons other than radiographic disease progression will have post-treatment follow-up imaging for disease status until disease progression is documented per PCWG-modified RECIST 1.1 and verified by blinded independent central review, the start of a new anticancer treatment, withdrawal of consent, death, or loss to follow-up. All participants will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study. The overall study ends when the last participant completes the last study-related contact or visit, withdraws from the study, or is lost to follow-up (ie, the participant is unable to be contacted by the investigator).

Study Governance Committees:

Executive Oversight Committee	Yes
Data Monitoring Committee	Yes
Clinical Adjudication Committee	No
Steering Committee	No

Study governance considerations are outlined in Appendix 1.

As of Amendment 04, the Executive Oversight Committee and Data Monitoring Committee are no longer applicable.

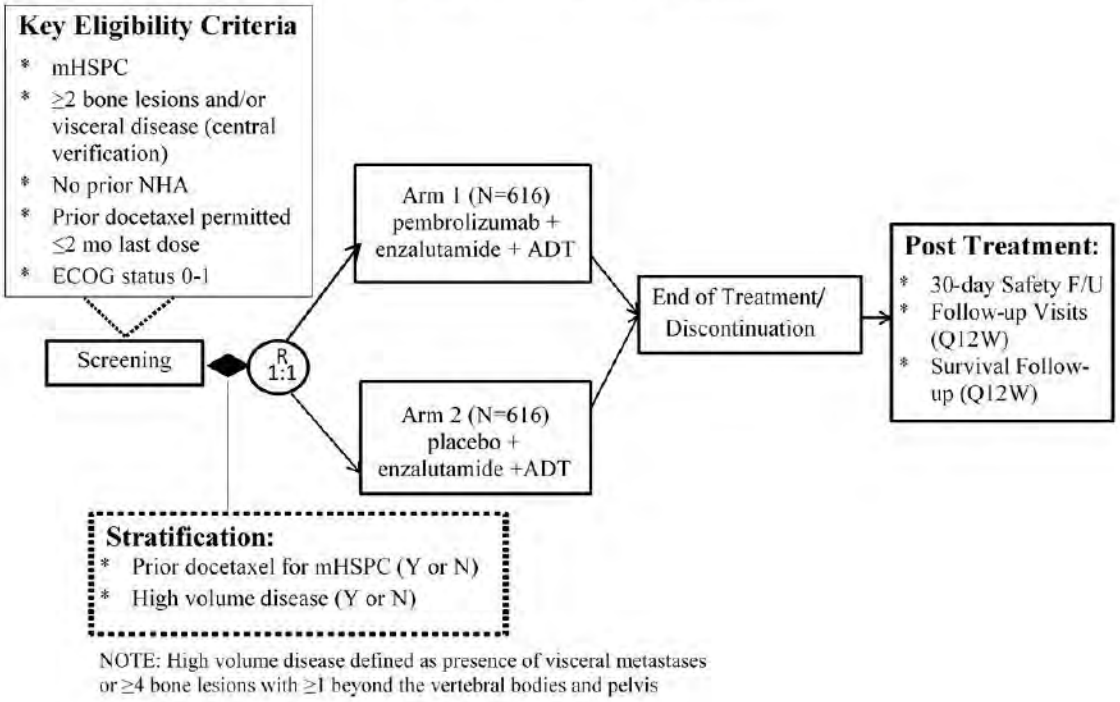
Study Accepts Healthy Volunteers: No

A list of abbreviations used in this document can be found in Appendix 10.

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 Study Schema



NOTE: High volume disease defined as presence of visceral metastases or ≥4 bone lesions with ≥1 beyond the vertebral bodies and pelvis

Pembrolizumab (200 mg Q3W)/placebo (Q3W) treatment will begin on Day 1 of each 3-week cycle and will continue for up to 35 cycles (approximately 2 years unless specific withdrawal/ discontinuation criteria are met). Enzalutamide (160 mg PO QD) treatment will begin on the same day as Day 1 Cycle 1 of pembrolizumab/placebo and will be continued on a daily dosing cycle until criteria for discontinuation are met (eg, disease progression). Participants who must discontinue 1 of the 2 treatments due to drug-related AEs may continue with the other combination partner until criteria for discontinuation are met.

Abbreviations: ADT androgen deprivation therapy (LHRH agonist or antagonist) or surgical castration (ie. Bilateral orchiectomy); ECOG Eastern Cooperative Oncology Group; mHSPC metastatic hormone-sensitive prostate cancer; N number; NHA next generation hormonal agents; PO per oral; Q12W every 12 weeks.

1.3 Schedule of Activites

Table 1 Initial Treatment Phase (Pembrolizumab/Placebo Plus Enzalutamide Plus ADT)

As of Amendment 04, participants who are still on study treatment will no longer collect central PSA blood samples, SSRE assessments, ePRO assessments (FACT-P, EQ-5D-5L, BPI-SF), CCI [redacted] or tumor response assessments by BICR. However, local tumor imaging assessments should continue per SOC schedule. In addition, Follow-up and Survival Follow-up visits will no longer be conducted.

Trial Period	Screening Phase	Treatment Cycles (21-day cycles)						End of Treatment	Post-Treatment			Notes
Treatment Cycle/Title	Screening (Visit 1)	1	2	3	4	5	6 to 35	EOT Visit	Safety Follow up	Follow up Visits	Survival Follow up	CCI [redacted]
Scheduling Window (Days)	42 to 1	+ 3	± 3	± 3	± 3	± 3	± 3	At pembro/ placebo Discon.	30 (+7) days from last dose	Q12W (± 7 days)	Q12W (± 7 days)	
Administrative Procedures												
Informed consent	X											
Inclusion/ exclusion criteria	X											
Participant identification card	X	X										
Demographics and medical history	X											

Trial Period	**Screening Phase**	**Treatment Cycles (21-day cycles)**						**End of Treatment**	**Post-Treatment**			**Notes**
Treatment Cycle/Title	Screening (Visit 1)	1	2	3	4	5	6 to 35	EOT Visit	Safety Follow up	Follow up Visits	Survival Follow up	CCI [redacted]
Scheduling Window (Days)	42 to 1	+ 3	± 3	± 3	± 3	± 3	± 3	At pembro/ placebo Discon.	30 (+7) days from last dose	Q12W (± 7 days)	Q12W (± 7 days)	
Prior and concomitant medication review	X	X	X	X	X	X	X	X	X			
HIV, Hep B, and Hep C status	X											
Randomization		X										
Telephone contact or visit (C1D8)		X										

Trial Period	**Screening Phase**	**Treatment Cycles (21-day cycles)**						**End of Treatment**	**Post-Treatment**			**Notes**
Treatment Cycle/Title	Screening (Visit 1)	1	2	3	4	5	6 to 35	EOT Visit	Safety Follow up	Follow up Visits	Survival Follow up	CCI [redacted]
Scheduling Window (Days)	42 to 1	+ 3	± 3	± 3	± 3	± 3	± 3	At pembro/ placebo Discon.	30 (+7) days from last dose	Q12W (± 7 days)	Q12W (± 7 days)	
Clinical Procedures/Assessments												
AE monitoring	X	X	X	X	X	X	X	X	X	X		
Full physical examination	X							X				
Directed physical examination		X	X	X	X	X	X		X			
Vital signs, height, and weight	X	X	X	X	X	X	X	X	X			

Trial Period	**Screening Phase**	**Treatment Cycles (21-day cycles)**						**End of Treatment**	**Post-Treatment**			**Notes**
Treatment Cycle/Title	Screening (Visit 1)	1	2	3	4	5	6 to 35	EOT Visit	Safety Follow up	Follow up Visits	Survival Follow up	CCI [redacted]
Scheduling Window (Days)	42 to 1	+ 3	± 3	± 3	± 3	± 3	± 3	At pembro/ placebo Discon.	30 (+7) days from last dose	Q12W (± 7 days)	Q12W (± 7 days)	
12 lead ECG	X											
ECOG performance status	X	X	X	X	X	X	X	X				
SSRE Assessment	X	X	X	X	X	X	X	X	X	X		
Subsequent anticancer therapy status									X	X	X	
Second progression											X	
Survival status		←									X	

Trial Period	**Screening Phase**	**Treatment Cycles (21-day cycles)**						**End of Treatment**	**Post-Treatment**			**Notes**
Treatment Cycle/Title	Screening (Visit 1)	1	2	3	4	5	6 to 35	EOT Visit	Safety Follow up	Follow up Visits	Survival Follow up	CCI [redacted]
Scheduling Window (Days)	42 to 1	+ 3	± 3	± 3	± 3	± 3	± 3	At pembro/ placebo Discon.	30 (+7) days from last dose	Q12W (± 7 days)	Q12W (± 7 days)	
Study Intervention Administration												
Pembrolizumab/ placebo		X	X	X	X	X	X					
Enzalutamide (dispensed/ returned)		X	X	X	X	X	X	X				

Trial Period	**Screening Phase**	**Treatment Cycles (21-day cycles)**						**End of Treatment**	**Post-Treatment**			**Notes**
Treatment Cycle/Title	Screening (Visit 1)	1	2	3	4	5	6 to 35	EOT Visit	Safety Follow up	Follow up Visits	Survival Follow up	CCI [redacted]
Scheduling Window (Days)	42 to 1	+ 3	± 3	± 3	± 3	± 3	± 3	At pembro/ placebo Discon.	30 (+7) days from last dose	Q12W (± 7 days)	Q12W (± 7 days)	
Laboratory Procedures/Assessments: analysis performed by CENTRAL laboratory												
PT or INR and PTT/aPTT	X											
Complete blood count with differential	X		X	X	X	X	X	X	X			
Comprehensive chemistry panel	X		X	X	X	X	X	X	X			
Urinalysis	X											
T3 or FT3, FT4, and TSH	X		X		X		X	X	X			

Trial Period	**Screening Phase**	**Treatment Cycles (21-day cycles)**						**End of Treatment**	**Post-Treatment**			**Notes**
Treatment Cycle/Title	Screening (Visit 1)	1	2	3	4	5	6 to 35	EOT Visit	Safety Follow up	Follow up Visits	Survival Follow up	CCI [redacted]
Scheduling Window (Days)	42 to 1	+ 3	± 3	± 3	± 3	± 3	± 3	At pembro/ placebo Discon.	30 (+7) days from last dose	Q12W (± 7 days)	Q12W (± 7 days)	
Testosterone	X				X		X	X				
Procedures/Assessments: analysis performed CENTRALLY												
Efficacy Measurements												
PSA by central laboratory	X	← Q3W (±7 days) from randomization through Week 12, then Q12W (± 7 days) thereafter →						X	X	X		

Trial Period	**Screening Phase**	**Treatment Cycles (21-day cycles)**						**End of Treatment**	**Post-Treatment**			**Notes**
Treatment Cycle/Title	Screening (Visit 1)	1	2	3	4	5	6 to 35	EOT Visit	Safety Follow up	Follow up Visits	Survival Follow up	CCI [redacted]
Scheduling Window (Days)	42 to 1	+ 3	± 3	± 3	± 3	± 3	± 3	At pembro/ placebo Discon.	30 (+7) days from last dose	Q12W (± 7 days)	Q12W (± 7 days)	
Tumor imaging (CT/MRI) and bone scan	X	Q12W (± 7 days) from randomization						X		X		
Tumor Tissue Collection/Correlative and Biomarker Studies: analysis performed by CENTRAL laboratory (refer to Appendix 7 for country-specific requirements)												
Tumor tissue collection	X											CCI [redacted]
CCI [redacted]		C C										

Trial Period	**Screening Phase**	**Treatment Cycles (21-day cycles)**						**End of Treatment**	**Post-Treatment**			**Notes**
Treatment Cycle/Title	Screening (Visit 1)	1	2	3	4	5	6 to 35	EOT Visit	Safety Follow up	Follow up Visits	Survival Follow up	CCI
Scheduling Window (Days)	42 to 1	+ 3	± 3	± 3	± 3	± 3	± 3	At pembro/ placebo Discon.	30 (+7) days from last dose	Q12W (± 7 days)	Q12W (± 7 days)	
CCI												
Patient-reported Outcomes												
BPI SF FACT P EQ 5D 5L	X	X	X	X	X	X	X	X	X			CCI

Trial Period	Screening Phase	Treatment Cycles (21-day cycles)						End of Treatment	Post-Treatment			Notes
Treatment Cycle/Title	Screening (Visit 1)	1	2	3	4	5	6 to 35	EOT Visit	Safety Follow up	Follow up Visits	Survival Follow up	CCI [redacted]
Scheduling Window (Days)	42 to 1	+ 3	± 3	± 3	± 3	± 3	± 3	At pembro/ placebo Discon.	30 (+7) days from last dose	Q12W (± 7 days)	Q12W (± 7 days)	
Treatment Eligibility Assessment (TEA)	X											

Abbreviations: AE adverse event; aPTT activated partial thromboplastin time; BICR blinded independent central review; BPI SF Brief Pain Inventory Short Form; CT computed tomography; CCI [redacted]; Discon discontinuation; CCI [redacted] ECG electrocardiogram; ECOG Eastern Cooperative Oncology Group; EOT end of treatment; EQ 5D 5L EuroQol 5 dimension, 5 level health state utility index; FACT P Functional Assessment of Cancer Therapy Prostate; FT3 free triiodothyronine; FT4 free thyroxine; Hep hepatitis; HIV human immunodeficiency virus; ICF informed consent form; INR international normalized ratio; IRB Institutional Review Board; IV intravenous; MRI magnetic resonance imaging; PD progressive disease; PD L1 programmed cell death ligand 1; PRO patient reported outcome; PSA prostate specific antigen; PT prothrombin time; PTT partial thromboplastin time; Q3W every 3 weeks; Q9W every 9 weeks; Q12W every 12 weeks; CCI [redacted]; SAE serious adverse event; SCF Sponsor Communication Form; SOC standard of care; SSRE symptomatic skeletal related event; TEA Treatment Eligibility Assessment ;T3 total triiodothyronine; TSH thyroid stimulating hormone; W week.

Table 2 Extension First Course Phase (Enzalutamide + ADT)

As of Amendment 04, participants who are still on study treatment will no longer collect central PSA blood samples, SSRE assessments, ePRO assessments (FACT-P, EQ-5D-5L, BPI-SF), CCI [redacted] r tumor response assessments by BICR. However, local tumor imaging assessments should continue per SOC schedule. In addition, Follow-up and Survival Follow-up visits will no longer be conducted.

Trial Period	Treatment Cycles (84-day cycles)	End of Treatment	Post-Treatment			Notes
Treatment Cycle/Title	Cycle 1 and beyond	EOT Visit	Safety Follow up	Follow up Visits	Survival Follow up	CCI [redacted]
Scheduling Window (Days)	Day 1 (± 7 days) of every cycle	At time of Discon	30 (+7) days from last dose	Q12W (± 7 days)	Q12W (± 7 days)	
Administrative Procedures						
Concomitant medication review	X	X	X			
Clinical Procedures Assessments						
AE monitoring	X	X	X	X		

Trial Period	**Treatment Cycles (84-day cycles)**	**End of Treatment**	**Post-Treatment**			**Notes**
Treatment Cycle/Title	Cycle 1 and beyond	EOT Visit	Safety Follow up	Follow up Visits	Survival Follow up	CCI [redacted]
Scheduling Window (Days)	Day 1 (± 7 days) of every cycle	At time of Discon	30 (+7) days from last dose	Q12W (± 7 days)	Q12W (± 7 days)	
Full physical examination		X				
Directed physical examination	X		X			
Vital signs, and weight	X	X	X			
ECOG performance status	X	X				
SSRE Assessment	X	X	X	X		
Subsequent anticancer therapy status			X	X	X	
Second progression					X	
Survival status	←	———	———	———	→	

Trial Period	Treatment Cycles (84-day cycles)	End of Treatment	Post-Treatment			Notes
Treatment Cycle/Title	Cycle 1 and beyond	EOT Visit	Safety Follow up	Follow up Visits	Survival Follow up	CCI [redacted]
Scheduling Window (Days)	Day 1 (± 7 days) of every cycle	At time of Discon	30 (+7) days from last dose	Q12W (± 7 days)	Q12W (± 7 days)	
Study Intervention Administration						
Enzalutamide (dispensed/returned)	X	X				
Laboratory Procedures/Assessments: analysis performed by CENTRAL laboratory						
PT or INR and PTT/aPTT	X					
Complete blood count with differential	X	X	X			
Comprehensive chemistry panel	X	X	X			
Urinalysis	X	X	X			CCI [redacted]
T3 or FT3, FT4, and TSH	X	X	X			
Testosterone	X	X				

Trial Period	Treatment Cycles (84-day cycles)	End of Treatment	Post-Treatment			Notes
Treatment Cycle/Title	Cycle 1 and beyond	EOT Visit	Safety Follow up	Follow up Visits	Survival Follow up	CCI [redacted]
Scheduling Window (Days)	Day 1 (± 7 days) of every cycle	At time of Discon	30 (+7) days from last dose	Q12W (± 7 days)	Q12W (± 7 days)	
Procedures/Assessments: analysis performed CENTRALLY						
Efficacy Measurements						
PSA by central laboratory	Q12W from randomization	X	X	X		CCI [redacted]
Tumor imaging (CT/MRI) and bone scan	Q12W from randomization	X		X		

Trial Period	Treatment Cycles (84-day cycles)	End of Treatment	Post-Treatment			Notes
Treatment Cycle/Title	Cycle 1 and beyond	EOT Visit	Safety Follow up	Follow up Visits	Survival Follow up	CCI [redacted]
Scheduling Window (Days)	Day 1 (± 7 days) of every cycle	At time of Discon	30 (+7) days from last dose	Q12W (± 7 days)	Q12W (± 7 days)	
Patient-Reported Outcomes						
BPI SF FACT P EQ 5D 5L	X	X	X			CCI [redacted]

Abbreviations: AE adverse event; aPTT activated partial thromboplastin time; BICR blinded independent central review; BPI SF Brief Pain Inventory Short Form; CT computed tomography; CTC circulating tumor cell; ctDNA circulating tumor deoxyribonucleic acid; Discon discontinuation; DNA deoxyribonucleic acid; ECG electrocardiogram; ECOG Eastern Cooperative Oncology Group; EOT end of treatment; EQ 5D 5L EuroQol 5 dimension, 5 level health state utility index; FACT P Functional Assessment of Cancer Therapy Prostate; FT3 free triiodothyronine; FT4 free thyroxine; Hep hepatitis; HIV human immunodeficiency virus; ICF informed consent form; INR international normalized ratio; IRB Institutional Review Board; IV intravenous; MRI magnetic resonance imaging; PD progressive disease; PD L1 programmed cell death ligand 1; PRO patient reported outcome; PSA prostate specific antigen; PT prothrombin time; PTT partial thromboplastin time; Q12W every 12 weeks; RNA ribonucleic acid; SAE serious adverse event; SCF Sponsor Communication Form; SOC standard of care; SSRE symptomatic skeletal related event; TEA Treatment Eligibility Assessment ;T3 total triiodothyronine; TSH thyroid stimulating hormone; W week.

Table 3 Second Course Phase (Pembrolizumab Retreatment ONLY)

NOTE: As of Amendment 04, Second Course treatment is not an option for participants. There are currently no participants in the Second Course Phase.

Trial Period	**Treatment Cycles (21-day cycles)**					**End of Treatment**	**Post-Treatment**			**Notes**
Treatment Cycle/Title	1	2	3	4	5 to 17	EOT Visit	Safety Follow up	Follow up Visits	Survival Follow up	CCI [redacted]
Scheduling Window (Days)		± 3	± 3	± 3	± 3	At time of Discon	30 (+7) days from last dose	Q12W (± 7 days)	Q12W (± 7 days)	
Administrative Procedures										
Eligibility criteria	X									
Concomitant medication review	X	X	X	X	X	X	X			CCI [redacted]
Clinical Procedures/Assessments										
AE monitoring	X	X	X	X	X	X	X	X		CCI [redacted]

Trial Period	Treatment Cycles (21-day cycles)					End of Treatment	Post-Treatment			Notes
Treatment Cycle/Title	1	2	3	4	5 to 17	EOT Visit	Safety Follow up	Follow up Visits	Survival Follow up	CCI [redacted]
Scheduling Window (Days)		± 3	± 3	± 3	± 3	At time of Discon	30 (+7) days from last dose	Q12W (± 7 days)	Q12W (± 7 days)	
Full physical examination	X					X				
Directed physical examination		X	X	X	X		X			
Vital signs and weight	X	X	X	X	X	X				CCI [redacted]
ECOG performance status	X	X	X	X	X	X				
Subsequent anticancer therapy status							X	X	X	
Survival status	←								X	

Trial Period	Treatment Cycles (21-day cycles)					End of Treatment	Post-Treatment			Notes
Treatment Cycle/Title	1	2	3	4	5 to 17	EOT Visit	Safety Follow up	Follow up Visits	Survival Follow up	CCI [redacted]
Scheduling Window (Days)		± 3	± 3	± 3	± 3	At time of Discon	30 (+7) days from last dose	Q12W (± 7 days)	Q12W (± 7 days)	
Study Intervention Administration										
Pembrolizumab	X	X	X	X	X					CCI [redacted]
Enzalutamide (dispensed/returned)	X	X	X	X	X	X				

Trial Period	Treatment Cycles (21-day cycles)					End of Treatment	Post-Treatment			Notes
Treatment Cycle/Title	1	2	3	4	5 to 17	EOT Visit	Safety Follow up	Follow up Visits	Survival Follow up	CCI [redacted]
Scheduling Window (Days)		± 3	± 3	± 3	± 3	At time of Discon	30 (+7) days from last dose	Q12W (± 7 days)	Q12W (± 7 days)	
Laboratory Procedures/Assessments: analysis performed by CENTRAL laboratory										
PT or INR and PTT/aPTT	X									
Complete blood count with differential	X	X	X	X	X	X	X			
Comprehensive chemistry panel	X	X	X	X	X	X	X			
Urinalysis	X									

Trial Period	Treatment Cycles (21-day cycles)					End of Treatment	Post-Treatment			Notes
Treatment Cycle/Title	1	2	3	4	5 to 17	EOT Visit	Safety Follow up	Follow up Visits	Survival Follow up	CCI [redacted]
Scheduling Window (Days)		± 3	± 3	± 3	± 3	At time of Discon	30 (+7) days from last dose	Q12W (± 7 days)	Q12W (± 7 days)	
T3 or FT3, FT4, and TSH	X		X		X	X	X			
Testosterone	X			X	X	X				
Procedures/Assessments: analysis performed by CENTRAL laboratory										
Efficacy Measurements										
PSA by central laboratory	X	◄——► Q3W (±7 days) from first retreatment infusion through Week 12, then Q12W (± 7 days) thereafter				X	X	X		

Trial Period	Treatment Cycles (21-day cycles)					End of Treatment	Post-Treatment			Notes
Treatment Cycle/Title	1	2	3	4	5 to 17	EOT Visit	Safety Follow up	Follow up Visits	Survival Follow up	CCI [redacted]
Scheduling Window (Days)		± 3	± 3	± 3	± 3	At time of Discon	30 (+7) days from last dose	Q12W (± 7 days)	Q12W (± 7 days)	
Tumor imaging (CT/MRI) and bone scan (evaluated locally)	X	← Q12W (± 7 days) from first retreatment infusion →				X		X		

Abbreviations: AE adverse event; aPTT activated partial thromboplastin time; CT computed tomography; Discon discontinuation; ECI events of clinical interest; ECOG Eastern Cooperative Oncology Group; EOT end of treatment; FT3 free triiodothyronine; FT4 free thyroxine; iCRO imaging contract research organization; INR international normalized ratio; MRI magnetic resonance imaging; PSA prostate specific antigen; PT prothrombin time; PTT partial thromboplastin time; Q3W every 3 weeks; Q12W every 12 weeks; SAE serious adverse event; T3 total triiodothyronine; TSH thyroid stimulating hormone.

2 INTRODUCTION

Prostate cancer represents the second most common malignancy diagnosed in men worldwide, with an estimated annual incidence of over 1 million and an expected 300,000 plus deaths annually [Ferlay, J., et al 2015]. In the US, approximately 1 in every 9 men will be diagnosed with prostate cancer in his lifetime [Siegel, R. L., et al 2018].

While many men diagnosed with locally confined disease may be treated definitively with radiation or surgery, approximately 30% of men have recurrent disease and go on to develop metastatic prostate cancer. In addition, 5% to 30% of men with prostate cancer have metastatic disease at initial diagnosis, a percentage that varies greatly by region, but is on an increasing trend that is expected to continue in the future [Cancer registration committee of the Japanese Urological Associa 2005] [Jack, R. H., et al 2010] [Scher, H. I., et al 2015] [Kelly, S. P., et al 2018] [Weiner, A. B., et al 2016] [Smith, S. 2018] [National Cancer Institute 2019]. Once prostate cancer has become metastatic there are no longer any curative treatments and expected median survival is less than 5 years. Patients with metastases have traditionally been treated first with ADT, usually with LHRH agonist or antagonist that results in suppression of testosterone production in the testes. This alone often succeeds in controlling disease for some time, years in many cases. However, prostate cancer progresses invariably and requires additional systemic therapies to re-establish control of disease.

Both docetaxel and abiraterone have been shown to prolong OS when combined upfront with ADT and are now considered standard of care for men diagnosed with high-volume or high-risk mHSPC. More recently, the second-generation androgen receptor inhibitors apalutamide and enzalutamide were examined in patients with mHSPC. Combination of apalutamide with ADT resulted in a significant improvement in both rPFS (HR 0.48, p<0.001) and OS (HR 0.67, p 0.005) compared to ADT alone [Chi, K. N., et al 2019]. The combination of enzalutamide with ADT was studied in two Phase 3 studies; one compared to ADT alone and the second compared to ADT plus a first-generation anti-androgen. In the first study (ARCHES), the addition of enzalutamide to ADT resulted in a significant improvement in rPFS (HR 0.39, p<0.0001), with the interim OS analysis being immature with 93% of patients still alive [Armstrong, A. J., et al 2019]. In the second study, the addition of enzalutamide to ADT resulted in a significant improvement in OS compared to ADT plus a first-generation anti-androgen (HR 0.67, p 0.0016) [Davis, I. D., et al 2019]. The efficacy of both apalutamide and enzalutamide were consistent across all subgroups, including patients with low- or high-volume disease, as well as those with de novo metastases or with metastases after failing primary therapy.

While these therapies are initially effective, patients invariably succumb to their disease and the effectiveness of subsequent therapies diminishes after progression on the prior therapy. Thus, there remains a significant unmet need for novel therapies or combination regimens for patients with metastatic prostate cancer.

2.1 Study Rationale

Bishop et al. demonstrated in a mouse xenograft model that enzalutamide-resistant tumors express significantly increased levels of tumor intrinsic PD-L1 compared to non enzalutamide-resistant tumors [Bishop, J. L., et al 2015]. Additionally, in a small cohort of participants, it was noted that those who progressed while on enzalutamide had a significantly increased number of PD-L1/ PD-L2 positive dendritic cells in their blood compared to treatment-naïve participants or participants who were responding to enzalutamide. Thus, by blocking the PD-1 receptor, pembrolizumab treatment may increase the immune response to enzalutamide-resistant cells that emerge in response to treatment with enzalutamide.

KEYNOTE-365 (KN365), an ongoing Phase 1b/2 umbrella study evaluating pembrolizumab combination therapies in mCRPC participants, included a Cohort C for the evaluation of pembrolizumab in combination with enzalutamide in participants who received prior abiraterone acetate in the pre-chemotherapy mCRPC state. As this was a patient population that had received prior abiraterone they were expected to have limited efficacy to enzalutamide alone. Interim results from Cohort C (data cutoff 27-JUL-2018) showed a confirmed PSA response (at least 50% reduction in PSA from baseline) in 26% (18/69) of participants, and a RECIST objective response (CR + PR) in 20% (5/25) of participants with measurable disease at baseline. Of note, these responses were independent of PD-L1 status. The PSA response rate was 6/20 (30%) and 11/44 (25%), for PD-L1 positive and PD-L1 negative patients respectively. The ORR per RECIST 1.1 was 2/9 (22.2%) and 2/15 (13.3%) for PD-L1 positive and PD-L1 negative patients with measurable disease at baseline, respectively. These results provide support for further evaluation of the combination of pembrolizumab and enzalutamide, and there is opportunity for improvement in the efficacy of the combination regimen if given at initiation of hormone therapy, due to the long-term effect of an immune response.

The present trial, KEYNOTE-991 (KN991) is a randomized, multicenter, double-blind, placebo-controlled, Phase 3 trial in participants with mHSPC. Participants will be randomly assigned 1:1 to treatment with either pembrolizumab + enzalutamide + ADT or placebo + enzalutamide + ADT.

2.2 Background

Pembrolizumab is a potent humanized IgG4 mAb with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and PD-L2. Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an IV immunotherapy for advanced malignancies. Keytruda® (pembrolizumab) is indicated for the treatment of patients across a number of indications. For more details on specific indications refer to the IB.

2.2.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades [Disis, M. L. 2010]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells/FoxP3+ T-regs correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer, hepatocellular carcinoma, malignant melanoma, and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma [Dudley, M. E., et al 2005] [Hunder, N. N., et al 2008].

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [Greenwald, R. J., et al 2005] [Okazaki, T., et al 2001].

The structure of murine PD-1 has been resolved [Zhang, X., et al 2004]. PD-1 and its family members are type I transmembrane glycoproteins containing an IgV type domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ, and ZAP70, which are involved in the CD3 T-cell signaling cascade [Okazaki, T., et al 2001] [Chemnitz, J. M., et al 2004] [Sheppard, K-A, et al 2004] [Riley, J. L. 2009]. The mechanism by which PD-1 down-modulates T-cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins [Parry, R. V., et al 2005] [Francisco, L. M., et al 2010]. As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in mHSPC.

2.2.2 Preclinical and Clinical Studies

Refer to the pembrolizumab IB for a summary of the preclinical and clinical experience with pembrolizumab.

2.2.3 Ongoing Clinical Studies in Prostate Cancer

KEYNOTE-199 (KN199) is an ongoing, Phase 2, nonrandomized, multinational, multi-cohort, open-label study of pembrolizumab in patients with mCRPC who received docetaxel-based chemotherapy and either abiraterone acetate or enzalutamide treatment. At the time of the data cutoff (21-AUG-2018), 199 patients were enrolled in the cohorts with

RECIST-measurable disease and PD-L1 status: 133 in PD-L1 positive and 66 PD-L1 negative. Overall ORR was 5% (95% CI, 2-11) for PD-L1-positive patients and 3% (95% CI, <1-11) for PD-L1-negative patients, with a DCR ≥6 months of 10% and 9%, respectively. Median OS was 9.5 months in PD-L1-positive patients and 7.9 months in PD-L1-negative patients. These results suggested potential efficacy, regardless of PD-L1 status, that warranted further evaluation. Additionally, early unpublished results from Graff et al suggest a potential survival benefit in the advanced mCRPC population with pembrolizumab monotherapy [Graff, J. N., et al 2016].

Graff et al[Graff, J. N., et al 2016], initially enrolled 10 men in 2015-2016 who had mCRPC with evidence of progression on enzalutamide, and subsequently enrolled a total of 28. Because previous immunotherapies (nivolumab, ipilimumab) had failed to produce an objective response in mCRPC [Topalian, S. L., et al 2012] [Kwon, E. D., et al 2014], interest in pursuing further studies waned. Nonetheless, after some success, Graff et al [Graff, J. N., et al 2018], undertook the Phase 2 study adding pembrolizumab to enzalutamide for men with mCRPC progressing on enzalutamide and reported a decline in PSA ≥50% (primary endpoint) in 5 of 28 patients (17.9%) and an OR (secondary endpoint) in 3 of 12 patients (25.0%) who had measurable disease at baseline. At last report, 3 of the 5 responders continued to respond (range, 21.9-33.8 months), and median OS was 22.2 months (95% CI, 14.7-28.4 months).

KN365, a Phase 2 umbrella study evaluating pembrolizumab combination therapies in mCRPC participants, included a cohort for the evaluation of pembrolizumab in combination with enzalutamide (Cohort C). Participants in this cohort were required to have had previously received abiraterone acetate. The primary endpoint is the percentage of participants with a decrease in PSA level of ≥50%. In a recent amendment of the protocol, ORR based on RECIST 1.1 by BICR was changed from a secondary endpoint to a (dual) primary endpoint. Additionally, the target enrollment in each of the three cohorts was expanded to 100, and a new cohort for pembrolizumab in combination with abiraterone acetate with target enrollment of 100 mCRPC patients was added. See Section 2.1 for a summary of interim results.

KN641 is a Phase 3 randomized, placebo-controlled study evaluating the efficacy and safety of pembrolizumab in combination with enzalutamide and ADT for the treatment of mCRPC. The study is enrolling participants in the pre-chemotherapy mCRPC state, with or without prior treatment with abiraterone acetate. Approximately 1200 participants will be randomized 1:1 to either pembrolizumab plus enzalutamide vs placebo plus enzalutamide. The dual primary endpoints are rPFS and OS.

For details on additional ongoing studies, including in other tumor types, please refer to the pembrolizumab IB.

2.2.4 Information on Other Study-related Therapy

Enzalutamide (Xtandi®) is an androgen receptor inhibitor indicated for the treatment of patients with mCRPC. Enzalutamide acts on different steps in the androgen receptor signaling pathway. Enzalutamide has been shown to competitively inhibit androgen binding

to androgen receptors and inhibit androgen receptor nuclear translocation and interaction with DNA. A major metabolite, N-desmethyl enzalutamide, exhibited similar in vitro activity to enzalutamide. Enzalutamide decreased proliferation and induced cell death of prostate cancer cells in vitro and decreased tumor volume in a mouse prostate cancer xenograft model. Refer to the approved labeling for detailed background information on enzalutamide.

For additional information on enzalutamide, refer to the approved product label.

2.3 Benefit/Risk Assessment

It cannot be guaranteed that participants in clinical studies will directly benefit from treatment during participation, as clinical studies are designed to provide information about the safety and effectiveness of an investigational medicine.

Pembrolizumab has been administered in a large number of cancer participants with a well characterized safety profile and has received regulatory approval for unresectable or metastatic melanoma, metastatic NSCLC, recurrent or metastatic HNSCC, advanced UC, MSI-H cancer, cHL, advanced gastric cancer, advanced cervical cancer, HCC, and PMBCL. Overall, pembrolizumab is well tolerated at doses up to 10 mg/kg every 2 weeks (Q2W). Pembrolizumab has also demonstrated anticancer clinical activity and efficacy in a broad range of cancer indications (see the pembrolizumab IB).

Enzalutamide has been approved by regulatory agencies globally for the treatment of CRPC and has been recommended for treatment for CRPC by NCCN and ESMO guidelines [Torre, L. A., et al 2016]. Adding enzalutamide upfront to ADT for patients with mHSPC has been evaluated in two recent Phase 3 studies and shown to improve efficacy when compared to treatment with ADT alone or ADT plus a first- generation anti-androgen (Section 2) [Armstrong, A. J., et al 2019] [Davis, I. D., et al 2019].

Preliminary results from Cohort C of KN365 (Section 2.1), in which participants with mCRPC were treated with the combination of pembrolizumab and enzalutamide, showed a confirmed RECIST objective response (CR + PR) in 20% (5/25) of participants with measurable disease at baseline, and a disease control rate (CR + PR + SD ≥6 months) of 34% (15/44). This is a patient population that had received prior abiraterone and thus expected to have limited efficacy to enzalutamide alone. In general, the safety and tolerability of pembrolizumab plus enzalutamide was consistent with the individual profiles of each agent. As of the most recent database lock (27-JUL-2018), 28 of 69 (41%) of participants had Grade 3 to 4 TRAEs, and there were no Grade 5 TRAEs. There was an increased incidence of all-Grade rash (23%) and Grade 3 rash (10%), which resolved with standard of care treatment.

Additional details regarding specific benefits and risks for participants participating in this clinical study may be found in the accompanying IB and informed consent documents.

NOTE: Based on the data from an interim safety and efficacy analysis for KEYNOTE-991 (data cutoff 31-OCT-2022), eDMC recommended stopping the study for futility because pembrolizumab in combination with enzalutamide and ADT did not demonstrate an improvement in OS or rPFS, the trial's dual primary endpoints, compared to placebo plus enzalutamide and ADT and appears unlikely to do so in a future analysis. Based upon these

data and the recommendation of the eDMC, the study was unblinded (as of 19-JAN-2023). All the prespecified interim analyses after IA1 and final analysis of the study described in the SAP will not be performed. Safety analysis will be performed at the end of the study; there will be no further analyses for efficacy and ePRO endpoints collected from participants beyond the IA1 cutoff date.

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

Hypotheses are aligned with objectives in the Objectives and Endpoints table.

In participants with mHSPC:

NOTE: Based on the data from an interim safety and efficacy analysis for KEYNOTE-991 (data cutoff 31-OCT-2022), eDMC recommended stopping the study for futility because pembrolizumab in combination with enzalutamide and ADT did not demonstrate an improvement in OS or rPFS, the trial's dual primary endpoints, compared to placebo plus enzalutamide and ADT and appears unlikely to do so in a future analysis. Based upon these data and the recommendation of the eDMC, the study was unblinded (as of 19-JAN-2023). All the prespecified interim analyses after IA1 and final analysis of the study described in the SAP will not be performed. Safety analysis will be performed at the end of the study; there will be no further analyses for efficacy and ePRO endpoints collected from participants beyond the IA1 cutoff date.

NOTE: In alignment with the study update memo sent to Investigators on 25-JAN-2023, all study participants should stop ongoing treatment with pembrolizumab/placebo. Exceptions may be requested for study participants who, in the assessment of their study physician, are benefitting from the combination of enzalutamide and pembrolizumab, after consulting with the Sponsor. All other study participants should be discontinued from study and be offered SOC treatment as deemed necessary by the Investigator. If enzalutamide as SOC is not accessible off study to the participant, central sourcing may continue. As of Amendment 04, participants who are still on study treatment will no longer collect central PSA blood samples, SSRE assessments, ePRO assessments (FACT-P, EQ-5D-5L, BPI-SF), CCI [redacted] **or tumor response assessments by BICR. However, local tumor imaging assessments should continue per SOC schedule. In addition, Follow-up and Survival Follow-up visits will no longer be conducted. Updated analyses are described in Section 9.**

Primary Objective	**Primary Endpoint**
To compare pembrolizumab plus enzalutamide plus ADT versus placebo plus enzalutamide plus ADT with respect to **rPFS** per PCWG-modified RECIST 1.1 as assessed by BICR where soft tissue will be assessed per RECIST 1.1 modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, and bone disease will be assessed per PCWG criteria. Hypothesis (H1): The combination of pembrolizumab plus enzalutamide plus ADT is superior to placebo plus enzalutamide plus ADT with respect to **rPFS** per PCWG-modified RECIST 1.1 as assessed by BICR.	**rPFS:** the time from randomization to radiographic progression or death due to any cause, whichever occurs first.
To compare pembrolizumab plus enzalutamide plus ADT versus placebo plus enzalutamide plus ADT with respect to **OS.** Hypothesis (H2): The combination of pembrolizumab plus enzalutamide plus ADT is superior to placebo plus enzalutamide plus ADT with respect to **OS.**	**OS**: the time from randomization to death due to any cause.
Secondary Objectives	**Secondary Endpoints**
To compare pembrolizumab plus enzalutamide plus ADT versus placebo plus enzalutamide plus ADT with respect to **TFST**. Hypothesis (H3): The combination of pembrolizumab plus enzalutamide plus ADT is superior to placebo plus enzalutamide plus ADT with respect to **TFST**.	**TFST:** the time from randomization to initiation of the first subsequent anticancer therapy or death, whichever comes first.
To compare pembrolizumab plus enzalutamide plus ADT versus placebo plus enzalutamide plus ADT with respect to **TTSSRE**.	**TTSSRE:** the time from randomization to the first SSRE, defined as: • use of EBRT to prevent or relieve skeletal symptoms

Hypothesis (H4): The combination of pembrolizumab plus enzalutamide plus ADT is superior to placebo plus enzalutamide plus ADT with respect to **TTSSRE**.	• occurrence of new symptomatic pathologic bone fracture (vertebral or non-vertebral) • occurrence of spinal cord compression • or tumor-related orthopedic surgical intervention, whichever occurs first
To assess pembrolizumab plus enzalutamide plus ADT versus placebo plus enzalutamide plus ADT with respect to the: - **Time to PSA progression** - **Time to radiographic soft tissue progression** per soft tissue rules of PCWG-modified RECIST 1.1, as assessed by BICR - **TTPP** - **PFS2** as determined by investigator assessment	**Time to PSA progression:** the time from randomization to PSA progression. The PSA progression date is defined as the date of 1) ≥25% increase and ≥2 ng/mL above the nadir, confirmed by a second value ≥3 weeks later if there is PSA decline from baseline, or 2) ≥25% increase and ≥2 ng/mL increase from baseline beyond 12 weeks if there is no PSA decline from baseline. **Time to radiographic soft tissue progression:** the time from randomization to radiographic soft tissue progression. **TTPP:** time from randomization to pain progression based on BPI-SF Item #3 "worst pain in 24 hours" and opioid use. **PFS2:** time from randomization to disease progression as determined by investigator assessment of radiological or clinical progression after next-line of therapy or death from any cause, whichever occurs first.
To assess pembrolizumab plus enzalutamide plus ADT versus placebo plus enzalutamide plus ADT with respect to the: - **PSA response rate** - **PSA undetectable rate** - **ORR and DOR per PCWG-modified RECIST 1.1 as assessed by BICR**	**PSA response:** a PSA decline of ≥50% from baseline measured twice at least 3 weeks apart **PSA undetectable:** PSA <0.2 ng/mL during study intervention **OR: CR** or **PR** **DOR:** the time from the earliest date of the first documented evidence of CR or PR until earliest date of disease progression or death due to any cause, whichever occurs first
To assess the **safety and tolerability** of pembrolizumab plus enzalutamide plus ADT versus placebo plus enzalutamide plus ADT.	**AEs** Study intervention discontinuation due to AEs

Tertiary/Exploratory Objectives	Tertiary/Exploratory Endpoints
CCI [redacted]	
To assess pembrolizumab plus enzalutamide plus ADT versus placebo plus enzalutamide plus ADT with respect to the change from baseline in scores for disease-related symptoms and HRQoL using the **BPI-SF, FACT-P and EQ-5D-5L questionnaires**	**BPI-SF:** progression in pain severity domain and change in pain interference domain **FACT-P:** FACT P total score, FACT-G total score, trial outcome index, functional well-being, physical well-being, prostate cancer subscore, and FACT Advanced Prostate Symptom Index 6 (FAPSI6) **EQ-5D-5L:** mobility, self-care, usual activities, pain/discomfort, and anxiety/depression health states and EQ-5D-5L visual analog scale (VAS)
CCI [redacted]	

4 STUDY

4.1 Overall Design

NOTE: Based on the data from an interim safety and efficacy analysis for KEYNOTE-991 (data cutoff 31-OCT-2022), eDMC recommended stopping the study for futility because pembrolizumab in combination with enzalutamide and ADT did not demonstrate an improvement in OS or rPFS, the trial's dual primary endpoints, compared to placebo plus enzalutamide and ADT and appears unlikely to do so in a future analysis. Based upon these data and the recommendation of the eDMC, the study was unblinded (as of 19-JAN-2023). All the prespecified interim analyses after IA1 and final analysis of the study described in the SAP will not be performed. Safety analysis will be performed at the end of the study; there will be no further analyses for efficacy and ePRO endpoints collected from participants beyond the IA1 cutoff date.

NOTE: In alignment with the study update memo sent to Investigators on 25-JAN-2023, all study participants should stop ongoing treatment with pembrolizumab/placebo. Exceptions may be requested for study participants who, in the assessment of their study physician, are benefitting from the combination of enzalutamide and pembrolizumab, after consulting with the Sponsor. All other study participants should be discontinued from study and be offered SOC treatment as deemed necessary by the Investigator. If enzalutamide as SOC is not accessible off study to the participant, central sourcing may continue. As of Amendment 04, participants who are still on study treatment will no longer collect central PSA blood samples, SSRE assessments, ePRO assessments (FACT-P, EQ-5D-5L, BPI-SF), CCI [redacted] **or tumor response assessments by BICR. However, local tumor imaging assessments should continue per SOC schedule. In addition, Follow-up and Survival Follow-up visits will no longer be conducted. Updated analyses are described in Section 9.**

This is a randomized, placebo-controlled, parallel-group, multi-site, double-blind/mask study of pembrolizumab plus enzalutamide plus ADT versus placebo plus enzalutamide plus ADT in participants with mHSPC.

Approximately 1232 participants will be randomly assigned in a 1:1 ratio to 1 of 2 treatment arms following a screening period of up to 42 days. There will be no planned crossover between treatment arms.

Arm 1: pembrolizumab 200 mg Q3W plus enzalutamide 160 mg QD plus ADT

Arm 2: placebo Q3W plus enzalutamide 160 mg QD plus ADT

Participant must maintain continuous ADT with a LHRH agonist or antagonist during study treatment or have a history of bilateral orchiectomy. Prior to randomization, participants will be stratified by prior treatment with docetaxel (yes vs no), and presence of high-volume disease (yes vs no).

Participants must have central verification of metastatic disease documented by either ≥2 bone lesions on bone scan and/or visceral disease (eg, lung or liver) by CT/MRI. Participants whose metastatic disease is limited to lymph nodes are not eligible. Up to 6 cycles of prior docetaxel therapy for mHSPC is permitted as long as the final treatment administration was completed within 2 months of randomization and there was no evidence of disease progression during or after completion of therapy. Prior treatment with a second-generation hormone agent, eg abiraterone, enzalutamide, apalutamide, or darolutamide, is not allowed.

Participants must provide a tumor tissue from a newly obtained core or excisional biopsy (obtained within 12 months of Screening) from soft tissue not previously irradiated (samples from tumors progressing in a prior site of radiation are allowed; other exceptions may be considered after Sponsor consultation). Participants with bone only or bone predominant disease may provide a bone biopsy sample (decalcification not allowed). However, if obtaining a new biopsy is not feasible, then participants may provide an archival tumor tissue sample after Sponsor consultation. Adequacy of these specimens for biomarker analysis will be evaluated by a central laboratory prior to randomization. For complete details about eligibility criteria, refer to Section 5.

Treatment with pembrolizumab/placebo may continue for up to 35 cycles (approximately 2 years starting with the first infusion in Cycle 1) or until meeting criteria for discontinuation of study intervention (Section 7.1). Treatment with enzalutamide will proceed continuously from Day 1 of Cycle 1 in both arms, unless criteria for discontinuation of study intervention are met (Section 7.1). If pembrolizumab/placebo is completed or discontinued for reasons other than progressive disease, participants still receiving enzalutamide will continue to receive enzalutamide and ADT (Extension First Course) until criteria for discontinuation are met (eg, disease progression).

Participants will be evaluated with radiologic imaging to assess response to treatment at regular intervals during the study (Section 8.2.1).

If a participant with radiographic progression is clinically stable or clinically improved, an exception may be considered to continue treatment upon consultation with the Sponsor.

AEs will be monitored throughout the study and graded in severity according to the guidelines outlined in the NCI CTCAE version 5.0. After the end of treatment, each participant will be followed for 30 days for AE monitoring. Serious adverse events (SAEs) will be collected for 90 days after the end of treatment or 30 days after the end of treatment if the participant initiates new anticancer therapy, whichever is earlier. Treatment-related SAEs must be reported regardless of the time point when they occur. Participants who discontinue treatment for reasons other than radiographic disease progression will continue study-related disease assessments until radiographic disease progression, initiating a cancer treatment, withdrawal of consent, or becoming lost to follow-up. All participants will be followed for survival. This will be done in a variety of ways including phone, email, chart review, or review of public records in compliance to local practices or regulations.

Second Course Treatment:

As of Amendment 04, second course treatment is not an option for participants. There are currently no participants in the Second Course Phase.

Participants who stop pembrolizumab as a result of obtaining an investigator-determined confirmed CR or those subjects who stop after receiving 35 cycles may be eligible for an additional 17 cycles (approximately 1 year) of pembrolizumab after BICR-verified progressive disease if they meet the criteria for retreatment (Second Course Phase) and the study is ongoing (Section 8.10.2.3). In this circumstance, unblinding to pembrolizumab versus placebo administration may occur on an individual basis and only after consultation with Sponsor Clinical Director as outlined in Section 8.1.10.1. Enzalutamide may be continued at the investigator's discretion during the Second Course treatment.

This study will use [redacted] using an independent, eDMC to monitor safety and efficacy during the course of the study. [redacted]. The results of the interim analyses will be reviewed by the eDMC, which will provide recommendations for the study in accordance with the eDMC Charter and the Statistical Analysis Plan (SAP) described in detail in Section 9 Statistical Analysis Plan.

Specific procedures to be performed during the study, as well as their prescribed times and associated visit windows, are outlined in the SOA in Section 1.3. Details of each procedure are provided in Section 8.

Extension Portion in China:

Approximately 186 participants in China will be randomized overall in the global portion and the China Extension Portion of the study. After enrollment of the global portion is closed, participants in China will continue to be enrolled and randomized in a 1:1 ratio in the Extension Portion designed to meet local regulatory requirements. The Extension Portion will be identical to the global portion (eg, double-blinded, with identical inclusion and exclusion criteria, study endpoints, primary and secondary objectives, randomization, and study procedures), with the exception of an additional supplemental statistical analysis plan (sSAP) section for participants enrolled in China. Details of the analysis will be provided in the sSAP.

4.2 Scientific Rationale for Study Design

This study is a randomized, double-blind, placebo-controlled study, a design selected to eliminate potential bias.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

The dual primary endpoints of the study will be rPFS and OS.

Radiographic PFS is an acceptable measure of clinical benefit for a late stage study that demonstrates superiority of a new antineoplastic therapy, especially if the magnitude of the effect is large and the therapy has an acceptable risk/benefit profile. The rPFS will be assessed by BICR according to PCWG-modified RECIST 1.1 (Section 8.2). Time-to-progression endpoints, including DOR and rPFS, will be measured until PD per PCWG-modified RECIST 1.1.

OS has been recognized as the gold standard for the demonstration of superiority of a new antineoplastic therapy in randomized clinical studies.

Time to initiation of the first subsequent anticancer therapy (TFST) and time to SSRE will be assessed as key secondary endpoints. TFST is supportive of rPFS as it incorporates reasons to switch therapies in addition to radiographic progression (eg, due to toxicity or clinical progression), thus providing a comprehensive measure of when an agent is considered no longer of clinical benefit. Symptomatic skeletal-related events are common in patients with prostate cancer due to the bone-predominance of the disease, and these events have significant, often debilitating, consequences for patients including pain, reduced quality of life and increased risk of death. Thus, a delay in the development of these events represents a clinically meaningful endpoint for patients with metastatic prostate cancer.

4.2.1.2 Safety Endpoints

Safety parameters frequently used for evaluating investigational-systemic anticancer treatments are included as safety endpoints including, but not limited to, the incidence of, causality, and outcome of AEs/SAEs, and changes in vital signs and laboratory values. AEs will be assessed as defined by CTCAE, Version 5.0.

4.2.1.3 Patient-reported Outcomes Assessments

Symptomatic improvement is considered a clinical benefit and accepted by health authorities as additional evidence of the risk-benefit profile of any new study intervention. In this study, HRQoL and disease-related symptoms will be investigated among all participants via the following assessment tools: BPI-SF, FACT-P and the EQ-5D-5L questionnaires.

The BPI-SF, FACT-P, and EQ-5D-5L PROs are not pure efficacy or safety endpoints because they are affected by both disease progression and study intervention tolerability.

The BPI-SF is a validated, 15-item domain-specific instrument designed to assess the severity of pain and the impact/interference of pain on daily functions [Cleeland, C. S. 2009a].

The FACT-P is a disease-specific 39-item questionnaire included for the purpose of assessing HRQoL and prostate cancer-specific symptoms. It is a well-established measure of HRQoL/health status commonly used in prostate cancer clinical studies. The FACT-P was developed specifically for patients with advanced prostate cancer and has been found to be reliable and valid in this population [Esper, P., et al 1997].

The EQ-5D-5L is a standardized instrument for use as a measure of health outcome and will provide data to develop health utilities for use in health economic analyses [Rabin, R. and de Charro, F. 2001]. This instrument has been used extensively in cancer studies and published results from these studies support its validity and reliability [Pickard, A. S., et al 2007].

CCI

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[redacted]

4.2.2 Rationale for the Use of Comparator/Placebo

Normal saline or dextrose infusion Q3W will be used as placebo for pembrolizumab. The use of saline or dextrose placebo in combination with enzalutamide will be used to maintain study blind and thus minimize any bias due to known treatment arm assignment. Normal saline is the primary diluent/placebo for pembrolizumab; use dextrose only if saline is not

available. The use of a placebo will allow for testing the hypotheses that rPFS for participants treated with pembrolizumab and enzalutamide is superior to the combination of placebo and enzalutamide in participants with mHSPC to be tested. Combination of enzalutamide with ADT has been shown to improve rPFS and OS in men with mHSPC compared to ADT alone and is thus considered an appropriate comparator in this study [Davis, I. D., et al 2019] [Armstrong, A. J., et al 2019].

4.3 Justification for Dose

4.3.1 Pembrolizumab

The planned dose of pembrolizumab for this study is 200 mg Q3W. Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is the appropriate dose of pembrolizumab for adults across all indications and regardless of tumor type. As outlined below, this dose is justified by the following:

- clinical data from 8 randomized studies demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg Q2W;
- clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications; and
- pharmacology data showing full target saturation in both systemic circulation (inferred from PK data) and tumor (inferred from PBPK analysis) at 200 mg Q3W.

Among the 8 randomized dose-comparison studies, a total of 2262 participants were enrolled with melanoma and NSCLC, covering different disease settings (treatment-naïve, previously treated, PD-L1 enriched, and all comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q3W (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2 and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5-fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating TMDD conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Second, a PBPK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumor.

Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other participant covariates on exposure, has shown that the fixed-dosing provides similar control of PK variability as weight-based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed-dose and 2 mg/kg Q3W dose. Supported by these PK characteristics and given that fixed-dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg Q3W fixed-dose was selected for evaluation across all pembrolizumab protocols.

4.3.2 Enzalutamide

The recommended dose of enzalutamide is 160 mg (four 40-mg capsules/tablets or two 80 mg tablets) administered orally QD. Refer to Section 6.6.2 and the approved labeling for detailed information regarding dose regimen/modification.

4.4 Beginning and End of Study Definition

The overall study begins when the first participant signs the ICF. The overall study ends when the last participant completes the last study-related telephone-call or visit, withdraws from the study, or is lost to follow-up (ie, the participant is unable to be contacted by the investigator).

For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory test result or at the time of final contact with the last participant, whichever comes last.

If the study includes countries in the European Economic Area (EEA), the local start of the study in the EAA is defined as First Site Ready (FSR) in any Member State.

4.4.1 Clinical Criteria for Early Study Termination

The clinical study may be terminated early if the extent (incidence and/or severity) of emerging effects/clinical endpoints is such that the risk/benefit ratio to the study population as a whole is unacceptable. In addition, further recruitment in the study or at (a) particular study site(s) may be stopped due to insufficient compliance with the protocol, GCP, and/or other applicable regulatory requirements, procedure-related problems or an unacceptably high number of discontinuations or withdrawals due to administrative reasons.

In the event of Sponsor decision to no longer supply study interventions, ample notification will be provided so that appropriate adjustments to participant treatment can be made.

5 STUDY POPULATION

As stated in the Code of Conduct for Clinical Trials (Appendix 1.1), this study includes participants of varying age (as applicable), race, ethnicity, and sex (as applicable). The collection and use of these demographic data will follow all local laws and guidelines in keeping with the needs for participant confidentiality guidelines while supporting the study of the disease, its related factors, and the IMP under investigation.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

A participant will be eligible for inclusion in the study if the participant meets all of the following criteria:

Type of Participant and Disease Characteristics

1. Has histologically- or cytologically-confirmed (if acceptable according to local health authority regulations) adenocarcinoma of the prostate without small cell histology. Diagnosis must be stated in a pathology report and confirmed by the investigator.
2. Has metastatic disease as assessed by investigator and verified by BICR (prior to randomization) by either ≥2 bone lesions on bone scan and/or visceral disease (eg, lung or liver) by CT/MRI. Participants whose metastatic disease is limited to lymph nodes are not eligible.
3. Once randomized, participant must be willing to maintain continuous ADT with a LHRH agonists or antagonists during study treatment or have a history of bilateral orchiectomy.
4. Has an ECOG performance status of 0 or 1 assessed within 10 days of randomization.
5. Participants receiving bone resorptive therapy (including, but not limited to, bisphosphonate or denosumab) must have been on stable doses for ≥4 weeks prior to randomization.
6. Demonstrates adequate organ function as defined in Table 4; all screening labs should be performed in central laboratory within 10 days of the first dose of study intervention.

Table 4 Laboratory Values for Adequate Organ Function

System	Laboratory Value
Hematological	
ANC	≥1500/µL
Platelets	≥100,000/µLa
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L[a]
Renal	
Creatinine OR Measured or calculated[b] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 × ULN OR ≥50 mL/min for participant with creatinine levels >1.5 × ULN
Hepatic	
Total bilirubin	≤1.5 ×ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN (≤5 × ULN for participants with liver metastases)
Coagulation	
INR or PT aPTT or PTT	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants

ALT (SGPT) = alanine aminotransferase (serum glutamic-pyruvic transaminase); ANC = absolute neutrophil count; aPTT = activated partial thromboplastin time; AST (SGOT) = aspartate aminotransferase (serum glutamic-oxaloacetic transaminase); CrCl = creatinine clearance; GFR = glomerular filtration rate; INR = International normalized ratio; PT = prothrombin time; PTT = partial thromboplastin time; ULN = upper limit of normal.

a. Hemoglobin and platelet requirements cannot be met by use of recent transfusion or growth factor support (GCSF or erythropoietin) within 2 weeks prior to randomization.

b. CrCl should be calculated per institutional standard.

Note: This table includes eligibility-defining laboratory value requirements for treatment; laboratory value requirements should be adapted according to local regulations and guidelines for the administration of specific chemotherapies.

Demographics

7. Is male, ≥18 years of age at the time of signing the informed consent.

Male Participants

Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

8. Male participants are eligible to participate if they agree to the following during the intervention period and for at least 120 days after the last dose of study intervention.
   - Refrain from donating sperm

     PLUS either:

   - Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent

     OR

   - Must agree to use contraception, unless confirmed to be azoospermic (vasectomized or secondary to medical cause [Appendix 5]), as detailed below:
     - Agree to use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant. Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile-vaginal penetration.

9. Male participants must agree to use male condom when engaging in any activity that allows for passage of ejaculate to another person of any sex.

Informed Consent

10. The participant (or legally acceptable representative if applicable) provides written informed consent/assent for the study

Additional Categories

11. Has provided newly obtained core or excisional biopsy (obtained within 12 months of Screening) from soft tissue not previously irradiated (samples from tumors progressing in a prior site of radiation are allowed; other exceptions may be considered after Sponsor consultation). Participants with bone only or bone predominant disease may provide a bone biopsy sample (decalcification not allowed). However, if obtaining a new biopsy is not feasible, then participants may provide an archival tumor tissue sample after Sponsor consultation (SCF). FFPE tissue blocks are preferred to slides. Newly obtained biopsies are preferred to archive tissue. Adequacy of these specimens for PD-L1 biomarker analysis will be required by a central laboratory prior to randomization.

    Note: Details pertaining to tumor tissue submission can be found in the Procedures Manual.

5.2 Exclusion Criteria

The participant must be excluded from the study if the participant meets any of the following criteria:

Medical Conditions

1. Has a known additional malignancy that is progressing or has required active treatment in the last 3 years. Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ that have undergone potentially curative therapy are not excluded.
2. Has an active autoimmune disease that has required systemic treatment in past 2 years (ie, with use of disease modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
3. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone or equivalent) or any other form of immunosuppressive therapy within 7 days prior the first dose of study intervention.
4. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the participant's participation for the full duration of the study, or is not in the best interest of the participant to participate, in the opinion of the treating investigator.
5. Has undergone major surgery including local prostate intervention (excluding prostate biopsy) within 28 days prior to randomization and not recovered adequately from the toxicities and/or complications.
6. Has a gastrointestinal disorder affecting absorption (eg, gastrectomy, active peptic ulcer disease within last 3 months).
7. Is unable to swallow tablets/capsules.
8. Has an active infection (including tuberculosis) requiring systemic therapy.
9. Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.
10. Has known active HIV, hepatitis B virus (eg, hepatitis B surface antigen reactive) or HCV (eg, HCV RNA [qualitative] is detected). Testing for Hepatitis B and Hepatitis C is not required unless mandated by local regulation.
11. Has known or suspected CNS metastases and/or carcinomatous meningitis.
12. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the study.
13. Has a history of seizure or any condition that may predispose to seizure (including, but not limited to prior cerebrovascular accident, transient ischemic attack, or brain arteriovenous malformation; or intracranial masses such as a schwannoma or meningioma that is causing edema or mass effect).
14. Has a history of loss of consciousness within 12 months of the Screening Visit.

15. Has had myocardial infarction or uncontrolled angina within 6 months prior to randomization.
    Note: Participants with recent history of revascularization for acute coronary syndrome within 3 months prior to randomization are included.
16. Has New York Heart Association class III or IV congestive heart failure or a history of New York Heart Association class III or IV congestive heart failure unless a screening echocardiogram or multigated acquisition scan performed within 3 months prior to randomization date demonstrates a left ventricular ejection fraction >45%.
17. Has a history of clinically significant ventricular arrhythmias (eg, ventricular tachycardia, ventricular fibrillation, torsades de pointes).
18. Has a history of Mobitz II second degree or third-degree heart block without a permanent pacemaker in place.
19. Has hypotension as indicated by systolic blood pressure <86 millimeters of mercury (mm Hg) at the Screening Visit.
20. Has bradycardia as indicated by a heart rate of <50 beats per minute on the Screening ECG.
21. Has uncontrolled hypertension as indicated by systolic blood pressure >170 mm Hg or diastolic blood pressure >105 mm Hg at the Screening Visit.
22. Has severe hypersensitivity (Grade ≥3) to pembrolizumab and/or any of its excipients.
23. Has hypersensitivity reaction to enzalutamide or any of its capsule components, including Labrasol, butylated hydroxyanisole, and butylated hydroxytoluene.

Prior/Concomitant Therapy

24. Has received any prior pharmacotherapy, radiation therapy or surgery for metastatic prostate cancer with the following exceptions:
    a. Up to 3 months of ADT with LHRH agonists or antagonists or orchiectomy with or without concurrent first-generation antiandrogens prior to randomization, with no radiographic evidence of disease progression or rising PSA prior to randomization if participant was not treated with docetaxel for metastatic prostate cancer.
    b. May have 1 course of palliative radiation or surgical therapy to treat symptoms resulting from metastatic disease if it was administered at least 4 weeks prior to randomization.
    c. For participants with low-volume metastatic disease (defined as <4 bone lesions), may have 1 course of definitive radiotherapy (ie, EBRT) to the prostate if it was administered at least 4 weeks prior to randomization.
    d. Up to 6 cycles of docetaxel therapy with final treatment administration completed within 2 months of randomization and no evidence of disease progression during or after completion of docetaxel therapy. In these participants, up to 6 months of ADT with LHRH agonists or antagonists or orchiectomy with or without concurrent first-generation antiandrogens is permitted.
25. Has received prior ADT as neoadjuvant/adjuvant therapy for non-metastatic prostate cancer for >39 months in duration or within 9 months prior to randomization or with evidence of disease progression while receiving ADT.

26. Has had prior treatment with a next generation hormonal agent (eg, abiraterone, enzalutamide, apalutamide, darolutamide).
27. Received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent, or with an agent directed to another stimulatory or coinhibitory T-cell receptor (eg, CTLA-4, OX-40, CD137).
28. Has used herbal products that may have hormonal anti-prostate cancer activity and/or are known to decrease PSA levels (eg, saw palmetto) within 4 weeks prior to randomization.
29. Has received treatment with 5-α reductase inhibitors (eg, finasteride, dutasteride), estrogens, cyproterone acetate and/or androgens within 4 weeks prior to randomization.
30. Has received a live vaccine within 30 days prior to randomization. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed. Refer to Section 6.5 for information on COVID-19 vaccines.

Prior/Concurrent Clinical Study Experience

31. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to randomization.

    Note: Participants who have entered the non-treatment Follow-up Phase of an investigational study may participate as long as it has been 4 weeks after the last dose of the previous investigational agent.

Other Exclusions

32. Has a "superscan" bone scan. This is defined as an intense symmetric activity in the bones and diminished renal parenchymal activity on baseline bone scan such that the presence of additional metastases in the future could not be evaluated.
33. Has had an allogeneic tissue/solid organ transplant.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

Participants should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea, or vomiting.

5.3.2 Contraception

Pembrolizumab may have adverse effects on a fetus in utero. Refer to Appendix 5 for approved methods of contraception.

Participants should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy of female partner were to occur during the study. In

order to participate in the study, participants with childbearing-potential female partners must adhere to the contraception requirement (Appendix 5) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 120 days after the last dose of study medication. If there is any question that a participant with childbearing-potential female partner will not reliably comply with the requirements for contraception, that participant should not be entered into the study.

5.3.3 Pregnancy

If a participant impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy must be reported to the Sponsor and followed as described in Section 8.4.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study, but are not subsequently randomized in the study. A minimal set of screen-failure information is required to ensure transparent reporting of screen-failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen-failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements as outlined in the data entry guidelines.

Participants may be rescreened up to two times after initially failing to meet the inclusion/exclusion criteria (refer to Section 8.10.1).

5.5 Participant Replacement Strategy

A participant who discontinues from study intervention OR withdraws from the study will not be replaced.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Clinical supplies (study interventions provided by the Sponsor) will be packaged to support enrollment. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

NOTE: In alignment with the study update memo sent to Investigators on 25-JAN-2023, all study participants should stop ongoing treatment with pembrolizumab/placebo. Exceptions may be requested for study participants who, in the assessment of their study physician, are benefitting from the combination of enzalutamide and pembrolizumab, after consulting with the Sponsor. All other study participants should be discontinued from study and be offered SOC treatment as deemed necessary by the Investigator. If enzalutamide as SOC is not accessible off study to the participant, central sourcing may continue.

The study intervention(s) to be used in this study are outlined in Table 5.

Country-specific requirements are noted in Appendix 7.

Table 5 Study Interventions

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
Arm 1	Experimental	Pembrolizumab	Biological/Vaccine	Solution	25 mg/mL	200 mg	IV Infusion	Day 1 of each 21-day cycle	Test Product	IMP	Central
Arm 1	Experimental	Enzalutamide	Drug	Capsule	40 mg/ 80 mg	160 mg	Oral	Four 40-mg capsules/ tablets orally per day/two 80 mg tablets orally per day	Test Product	IMP	Central
Arm 2	Active Comparator	Enzalutamide	Drug	Capsule	40 mg/ 80 mg	160 mg	Oral	Four 40-mg capsules/ tablets orally per day/two 80 mg tablets orally per day	Test Product	IMP	Central
Arm 2	Active Comparator	Placebo	Drug	Solution	NA	NA	IV Infusion	Day 1 of each 21-day cycle	Placebo	IMP	Local

EEA European Economic Area; IMP investigational medicinal product; IV intravenous; NA not applicable; NIMP/AxMP noninvestigational/auxiliary medicinal product.

The classification of IMP and NIMP/AxMP in this table is based on guidance issued by the European Commission and applies to countries in the EEA. Country differences with respect to the definition/classification of IMP and NIMP/AxMP may exist. In these circumstances, local legislation is followed.

In this protocol, placebo for pembrolizumab is diluent alone (normal saline and/or dextrose); diluent is used for blinding purposes and does not contain active ingredients. Normal saline is the primary diluent/placebo for pembrolizumab; use dextrose only if saline is not available.

All study interventions will be administered on an outpatient basis.

All products indicated in Table 5 will be provided centrally by the Sponsor with the exception of placebo which will be provided locally.

All participants will also receive and remain on a stable regimen of ADT (LHRH agonist or antagonist) or have surgical castration. Dose and frequency of administration will be consistent with local product label and should not change during the study.

Refer to Section 8.1.8 for details regarding administration of the study intervention.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

Details on preparation and administration of pembrolizumab are provided in the Pharmacy Manual.

6.2.2 Handling, Storage, and Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

For all study sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product (if applicable) as per local guidelines unless otherwise instructed by the Sponsor.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of study interventions in accordance with the protocol and any applicable laws and regulations.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Intervention randomization will occur centrally using an IRT system. There are 2 study intervention arms. Participants will be randomly assigned in a 1:1 ratio to pembrolizumab + enzalutamide + ADT or placebo + enzalutamide + ADT, respectively.

6.3.2 Stratification

Randomization will be stratified according to the following factors:

- Prior docetaxel for mHSPC: Yes vs No

  NOTE: Up to 6 cycles of docetaxel therapy for mHSPC is permitted as long as final treatment administration is completed within 2 months of randomization and no evidence of disease progression during or after completion of therapy.
- Presence of high-volume disease: Yes vs No

  NOTE: High-volume disease is defined as presence of visceral metastases OR ≥4 bone lesions with ≥1 beyond the vertebral bodies and pelvis.

6.3.3 Blinding

As of IA1, the study was unblinded. The subsection below is retained for reference.

A double-blinding technique with in-house blinding will be used. Pembrolizumab and placebo will be prepared and/or dispensed in a blinded fashion by an unblinded pharmacist or qualified site personnel so that the blind is maintained. The participant, the investigator, and Sponsor personnel or delegate(s) who are involved in the study intervention administration or clinical evaluation of the participants are unaware of the intervention assignments.

The treatment identity of enzalutamide will be open-label; the identity of those treatments will be known by the participant, the investigator, the Sponsor, and delegate(s) who are involved in study intervention administration or the clinical evaluation of participants.

See Section 8.1.10 for a description of the method of unblinding a participant during the study should such action be warranted.

PD-L1 and PSA results are not reported back to sites to prevent early withdrawal of participants from study intervention.

6.4 Study Intervention Compliance

Refer to Section 6.6.3 for Dose Modification and Toxicity Management Guidelines for irAEs associated with pembrolizumab monotherapy, coformulations, or IO combinations and for other allowed dose interruptions.

Administration of pembrolizumab/placebo will be monitored by the investigator and/or study staff. The total volume of study medication infused will be compared with the total volume prepared to determine compliance with each dose administered.

Interruptions from the protocol-specified treatment plan for more than 12 weeks between pembrolizumab doses for nondrug-related or administrative reasons require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

For enzalutamide, the site will validate compliance with study intervention at each site visit according to their standard operating procedure. If doses are missed or vomited, this must be indicated in the source documents and CRFs.

6.5 Concomitant Therapy

6.5.1 Prohibited Concomitant Therapy

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any medication or vaccination specifically prohibited, discontinuation from study therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Sponsor's Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study intervention requires the mutual agreement of the investigator, the Sponsor, and the participant.

Participants are prohibited from receiving the following concomitant therapies during the Treatment Phase of this study:

- Antineoplastic systemic chemotherapy, targeted or biological therapy not specified in this protocol (except denosumab and biphosphonate for bone metastases as standard of care if on stable doses >4 weeks prior to randomization)
- Immunotherapy not specified in this protocol
- Investigational agents not specified in this protocol
- Initiation of bone resorptive therapy including but not limited to denosumab (unless approved by Sponsor consultation)
- Radiation therapy

  Note: Palliative localized radiation therapy to a site of pre-existing disease may be permitted while on study after consultation with Sponsor. The radiation treatment field may not include a target lesion by RECIST 1.1.

- Live vaccines within 30 days prior to the first dose of study intervention and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.

  Note: If precluded by local regulations, live vaccines should not be given for 120 days after the last dose of pembrolizumab is administered.

  Any licensed COVID-19 vaccine (including for Emergency Use) in a particular country is allowed in the study as long as they are mRNA vaccines, replication-incompetent adenoviral vaccines, or inactivated vaccines. These vaccines will be treated just as any other concomitant therapy.

  Investigational vaccines (i.e., those not licensed or approved for Emergency Use) are not allowed.

- Systemic glucocorticoids for any purpose other than to modulate symptoms from an AE that is suspected to have an immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.
  Note: The following uses of corticosteroids are permitted without Sponsor consultation:

  - Inhaled steroids for management of asthma
  - Prophylactic corticosteroids to avoid allergic reactions (eg, IV contract dye)
  - Palliative prednisone up to 10 mg daily or corticosteroid equivalent in the manner used to treat men with prostate cancer
  - Physiologic doses of corticosteroids for adrenal insufficiency
  - Intranasal steroids for allergies

- 5-α reductase inhibitors (eg, finasteride, dutasteride), estrogens, and/or cyproterone

- Strong CYP2C8 inhibitors or strong CYP3A4 inducers should be avoided. However, if these medications are necessary and cannot be avoided then enzalutamide dose should be adjusted as indicated in the approved product label. Enzalutamide is a strong CYP3A4 inducer and a moderate CYP2C9 and CYP2C19 inducer. Concomitant use of enzalutamide with narrow therapeutic index drugs that are metabolized by CYP3A4 (eg, alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus), CYP2C9 (eg, phenytoin, warfarin), and CYP2C19 (eg, S-mephenytoin, clopidogrel) should be avoided if possible as enzalutamide may decrease their exposure. If coadministration with warfarin cannot be avoided, conduct additional INR monitoring.

  Note: a list of strong/moderate inducers of CYP3A4 can be found at the following website:

  https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#table2-2.

In addition to the medications listed here, site staff should refer to the local approved product label for permitted and prohibited medications, as well as drug-drug interactions for enzalutamide. Caution should be used if participants are receiving concomitant medications that may lower the seizure threshold.

The Exclusion Criteria describe other medications which are prohibited in this study.

All treatments that the investigator considers necessary for a participant's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the eCRF including all prescription, OTC products, herbal supplements, and IV medications and fluids. If changes occur during the study period, documentation of drug dosage, frequency, route, and date should also be included on the eCRF.

All concomitant medications received within 28 days prior to the first dose of study intervention and up to 30 days after the last dose of study intervention should be recorded. All concomitant medications administered during SAEs or ECIs are to be recorded. SAEs and ECIs are defined in Section 8.4.

6.5.2 Rescue Medications and Supportive Care

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator.

Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Table 7. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts

should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab, the investigator does not need to follow the treatment guidance. Refer to Table 7 in Section 6.6.3 for guidelines regarding dose modification and supportive care.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

6.6 Dose Modification (Escalation/Titration/Other)

6.6.1 Concomitant Combination Therapy

If either pembrolizumab/placebo is interrupted for >12 weeks (immune-related AE) or >3 consecutive weeks for administrative reasons or enzalutamide is interrupted for 28 consecutive days, the site must gain approval from the Sponsor to continue the other partner drug. Participants who must discontinue 1 of the 2 drugs in the combination due to drug-related AEs may continue with the other combination partner following consultation with the Sponsor until criteria for discontinuation of treatment are met.

All participants should remain on a stable regimen of ADT consistent with prescribing information and only adjusted if clinically indicated to achieve or maintain sub-castrate levels of testosterone (<50 ng/dL).

6.6.2 Dose Modification for Enzalutamide

If a participant experiences any Grade ≥3 toxicity related to enzalutamide treatment, the drug should be withheld until the toxicity decreases to Grade ≤2. Enzalutamide can then be resumed at the reduced dose of 120 mg daily. For repeat Grade ≥3 toxicity, it can again be held until toxicity decrease to Grade ≤2 and resumed at the reduced dose of 80 mg daily. Reduction below 80 mg is not allowed (Table 6).

Once the dose has been reduced, it may not be escalated up to a previous dose level.

Enzalutamide should be permanently discontinued in participants who develop a seizure while on treatment.

Posterior reversible encephalopathy syndrome (PRES) has been observed in participants treated with enzalutamide. This may present with rapidly evolving symptoms of seizure, lethargy, headache, confusion, blindness or visual disturbances, or other neurologic symptoms. Hypertension may or may not be present. Posterior reversible encephalopathy syndrome is diagnosed by brain imaging (preferably MRI). Enzalutamide should be withheld if PRES is suspected and then discontinued if a PRES diagnosis is confirmed.

Pembrolizumab/placebo should be interrupted if PRES or seizure is observed and may be resumed in these participants after consultation with the Sponsor.

Participants should be directed to report the development of rash regardless of severity promptly to investigators. Participants with rash should be treated promptly with steroids and dose interruption per protocol and monitored closely for worsening of rash which may require additional treatment.

In cases where both enzalutamide and pembrolizumab are interrupted, after resolution of the toxicity, the participant should first resume treatment with enzalutamide, and if tolerated, then pembrolizumab infusions can resume.

Table 6 Enzalutamide Dose Modification Guidelines for Drug-Related Adverse Events

Drug	Dose/Potency	Dose Frequency	Regimen
Initial enzalutamide dose	160 mg	QD	Four 40-mg capsules/tablets or two 80-mg tablets
First dose reduction	120 mg	QD	Three 40-mg capsules/tablets
Second dose reduction	80 mg	QD	Two 40-mg capsules/tablets or one 80-mg tablet
Abbreviations: QD every day			

6.6.3 Immune-Related Events and Dose Modification (Withhold, Treat, Discontinue)

Dose Modification and Toxicity Management for Immune-related AEs Associated With Pembrolizumab

AEs associated with pembrolizumab exposure may represent an immune-related response. These irAEs may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids, and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation.

Dose Modification and Toxicity Management Guidelines for irAEs associated with pembrolizumab monotherapy, coformulations, or IO combinations are provided in Table 7.

Table 7 Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated With Pembrolizumab Monotherapy, Coformulations, or IO Combinations

General instructions:

1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. Pembrolizumab monotherapy, coformulations, or IO combinations must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last treatment.
3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.
4. If pembrolizumab monotherapy, coformulations, or IO combinations have been withheld, treatment may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations, or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, or Grade 3 or 4	Permanently discontinue		
Diarrhea/Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus) • Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations, or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
AST or ALT Elevation or Increased Bilirubin	Grade 2[a]	Withhold	• Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3[b] or 4[c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	
T1DM or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold[d]	• Initiate insulin replacement therapy for participants with T1DM • Administer antihyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[d]		
Hyperthyroidism	Grade 2	Continue	• Treat with nonselective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue[d]		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations, or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Hypothyroidism	Grade 2	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue[d]		
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	• Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Neurological Toxicities	Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Asymptomatic cardiac enzyme elevation with clinical suspicion of myocarditis (which was previously myocarditis Grade 1 using CTCAE v4.0)	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations, or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
All Other irAEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event[e]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

AE(s) adverse event(s); ALT alanine aminotransferase; AST aspartate aminotransferase; CTCAE Common Terminology Criteria for Adverse Events; DRESS Drug Rash with Eosinophilia and Systemic Symptom; GI gastrointestinal; IO immuno oncology; ir immune related; IV intravenous; SJS Stevens Johnson Syndrome; T1DM type 1 diabetes mellitus; TEN Toxic Epidermal Necrolysis; ULN upper limit of normal.

Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.

[a] AST/ALT: >3.0 to 5.0 × ULN if baseline normal; >3.0 to 5.0 × baseline, if baseline abnormal; bilirubin:>1.5 to 3.0 × ULN if baseline normal; >1.5 to 3.0 × baseline if baseline abnormal

[b] AST/ALT: >5.0 to 20.0 × ULN, if baseline normal; >5.0 to 20.0 × baseline, if baseline abnormal; bilirubin:>3.0 to 10.0 × ULN if baseline normal; >3.0 to 10.0 × baseline if baseline abnormal

[c] AST/ALT: >20.0 × ULN, if baseline normal; >20.0 × baseline, if baseline abnormal; bilirubin: >10.0 × ULN if baseline normal; >10.0 × baseline if baseline abnormal

[d] The decision to withhold or permanently discontinue pembrolizumab monotherapy, coformulations, or IO combinations is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab monotherapy, coformulations, or IO combinations may be resumed.

[e] Events that require discontinuation include, but are not limited to encephalitis and other clinically important irAEs (eg, vasculitis and sclerosing cholangitis)

Dose Modification and Toxicity Management of Infusion Reactions Related to Pembrolizumab

Pembrolizumab may cause severe or life-threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 8.

Table 8 Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	Stop Infusion Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug intervention.	Participant may be premedicated 1.5 h (±30 minutes) prior to infusion of study intervention with: Diphenhydramine 50 mg PO (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg PO (or equivalent dose of analgesic).

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grades 3 or 4 Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	Stop Infusion. Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. Participant is permanently discontinued from further study drug intervention.	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov		

Other Allowed Dose Interruption for Pembrolizumab

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical / surgical events or logistical reasons not related to study therapy. Participants should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the participant's study record.

6.6.4 Management of Overlapping Toxicities

Based on the known toxicity profiles of pembrolizumab and enzalutamide, certain treatment-related AEs are uniquely associated with one drug versus the other. For example, seizure is a known risk for enzalutamide treatment, while immune-related AEs are risks for pembrolizumab treatment. However, certain AEs, such as diarrhea, may be initially considered attributable to either study intervention. Therefore, evaluation of attribution is important for determining the study intervention most likely related to the AE, or an alternative etiology, and subsequently proper clinical management. The following aspects should be considered:

1. Timing of AE onset:

   Since enzalutamide is dosed daily and continuously due to a relatively short half-life (5.8 days), and pembrolizumab is dosed Q3W due to a long half-life, enzalutamide can be interrupted to assess whether an AE improves/resolves with dechallenge (ie, interruption of treatment) based on the following 2 scenarios:

   - If an AE is identified during a treatment cycle (ie, between 2 pembrolizumab doses), consider whether only enzalutamide dose interruption is needed.
   - If an AE is identified at the beginning of a treatment cycle, pembrolizumab should be held, and enzalutamide interrupted based on severity and causality assessment.

     If the participant recovers from an AE in response to enzalutamide interruption (ie, positive dechallenge), the event is more likely to be related to enzalutamide. Otherwise, after excluding other alternative explanations, an immune-related AE should be considered. In cases where both enzalutamide and pembrolizumab are interrupted due to toxicity, enzalutamide should be resumed first, and if tolerated, then pembrolizumab infusions can resume.

2. Severity of AE:

   If an AE is suspected to be treatment-related and is severe/life-threatening at the time of onset or is rapidly worsened, action including interrupting both drugs and initiating treatment with a corticosteroid (with exception of hypothyroidism, Type 1 diabetes mellitus) and other supportive care should be taken promptly.

6.7 Intervention After the End of the Study

There is no study-specified intervention following the end of the study.

6.8 Clinical Supplies Disclosure

The emergency unblinding call center will use the intervention/randomization schedule for the study to unblind participants and to unmask study intervention identity. The emergency unblinding call center should only be used in cases of emergency (see Section 8.1.10). In the event that the emergency unblinding call center is not available for a given site in this study, the central electronic (IRT) should be used to unblind participants and to unmask study intervention identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

6.9 Standard Policies

Trial site personnel will have access to the IRT system to allocate participants, to assign intervention to participants and to manage the distribution of clinical supplies. Each person accessing the IRT system must be assigned an individual unique PIN. They must use only their assigned PIN to access the system, and they must not share their assigned PIN with anyone.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

Discontinuation of study intervention does not represent withdrawal from the study.

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention prior to completion of the protocol-specified treatment period/vaccination regimen will still continue to participate in the study as specified in Section 1.3 and Section 8.10.3.

Participants may discontinue study intervention at any time for any reason or be dropped from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study intervention discontinuation are provided in Section 8.10.2.2.

A participant must be discontinued from study intervention, but continue to be monitored in the study for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- The participant interrupts pembrolizumab or placebo administration for more than 12 consecutive weeks for an irAE without Sponsor consultation.
- The participant has missed 28 consecutive days of enzalutamide without Sponsor consultation.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.
- The participant requires any medication or vaccination specifically prohibited in this study (Section 6.5.1).

- BICR-verified radiographic disease progression outlined in Section 8.2.1 (exception if the Sponsor approves treatment continuation following PD).

  - **As of Amendment 04, central tumor response assessments will no longer be performed. Participants on study treatment will be assessed locally by the investigator for disease progression per SOC schedule. Participants with PD per local investigator assessment should be discontinued (exception if the Sponsor approves treatment continuation following PD).**

- Any progression or recurrence of any secondary malignancy, or any occurrence of another malignancy that requires active treatment.

- Discontinuation of pembrolizumab/placebo may be considered for participants who have attained a confirmed CR and have been treated for at least 8 cycles (at least 24 weeks), receiving 2 cycles of pembrolizumab/placebo beyond the date when the initial CR was declared (does not apply to enzalutamide). These participants may be eligible for second course treatment described in Section 8.10.2.3.

- Completion of 35 cycles (approximately 2 years) with pembrolizumab/placebo (does not apply to enzalutamide).

  Note: The number of treatments is calculated starting with the first dose. Participants who stop pembrolizumab after receiving 35 doses may be eligible for retreatment if they progress after stopping pembrolizumab provided they meet the requirements detailed in Section 8.10.2.3. Participants may be retreated in the Second Course Phase (Retreatment) for up to an additional 17 cycles (approximately 1 year).

7.2 Participant Withdrawal From the Study

A participant must be withdrawn from the study if the participant or participant's legally acceptable representative withdraws consent from the study.

If a participant withdraws from the study, they will no longer receive study intervention or be followed at scheduled protocol visits.

Specific details regarding procedures to be performed at the time of withdrawal from the study, are outlined in Section 8.1.9. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

7.3 Lost to Follow-up

If a participant fails to return to the clinic for a required study visit and/or if the site is unable to contact the participant, the following procedures are to be performed:

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.
- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.

  Note: A participant is not considered lost to follow-up until the last scheduled visit for the individual participant. The missing data for the participant will be managed via the prespecified statistical data handling and analysis guidelines.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff. Delegation of study-site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).
- All study-related medical decisions must be made by an investigator who is a qualified physician.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, Hepatitis C), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

The maximum amount of blood collected from each participant over the duration of the study is provided in the Procedures Manual.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Administrative and General Procedures

8.1.1 Informed Consent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented consent from each potential participant (or each participant's legally acceptable representative) prior to participating in a clinical study. If there are changes to the participant's status during the study (eg, health or age of majority requirements), the investigator or medically qualified designee must ensure the appropriate consent is in place.

8.1.1.1 General Informed Consent

Consent must be documented by the participant's dated signature or by the participant's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the participant before participation in the study.

The initial ICF, any subsequent revised written ICF, and any written information provided to the participant must receive the IRB/IEC's approval/favorable opinion in advance of use. The participant or their legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's dated signature or by the participant's legally acceptable representative's dated signature.

The participant or their legally acceptable representative will be asked to sign consent after BICR-verified disease progression if continuing on study treatment. **As of Amendment 04, disease progression will no longer be centrally verified, participants will only be assessed locally.**

Specifics about a study and the study population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB/IEC requirements, applicable laws and regulations, and Sponsor requirements.

8.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator, who is a qualified physician, to ensure that the participant qualifies for the study.

8.1.3 Participant Identification Card

All participants will be given a participant identification card identifying them as participants in a research study. The card will contain study-site contact information (including direct telephone numbers) to be used in the event of an emergency. The investigator or qualified designee will provide the participant with a participant identification card immediately after the participant provides written informed consent. At the time of intervention randomization, site personnel will add the treatment/randomization number to the participant identification card.

The participant identification card also contains contact information for the emergency unblinding call center so that a healthcare provider can obtain information about study intervention in emergency situations where the investigator is not available.

8.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. The medical history will collect all active conditions and any condition diagnosed within the prior 10 years that the investigator considers to be clinically significant. Details regarding the disease for which the participant has enrolled in this study will be recorded separately and not listed as medical history.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 28 days before starting the study. Treatment for the disease for which the participant has enrolled in this study will be recorded separately and not listed as a prior medication.

8.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study through the Safety Follow-up Visit. In addition, new medications started during the Second Course Phase through the Second Course Safety Follow-up Visit should be recorded.

8.1.6 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur prior to randomization. Each participant will be assigned only 1 screening number. Screening numbers must not be re-used for different participants.

Any participant who is screened multiple times will retain the original screening number assigned at the initial Screening Visit. Participants may be rescreened up to two times after initially failing to meet the inclusion/exclusion criteria. Specific details on the screening/rescreening visit requirements are provided in Section 8.10.1.

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8.1.7 Assignment of Treatment/Randomization Number

All eligible participants will be randomly allocated and will receive a treatment/randomization number. The treatment/randomization number identifies the participant for all procedures occurring after treatment randomization. Once a treatment/randomization number is assigned to a participant, it can never be re-assigned to another participant.

A single participant cannot be assigned more than 1 treatment/randomization number.

8.1.8 Study Intervention Administration

Administration of pembrolizumab/placebo will be monitored by the investigator and/or study staff.

On Day 1 of each cycle, study intervention should be administered after all procedures and assessments have been completed. Study intervention can be administered ±3 days of the targeted Day 1 for each cycle, except Cycle 1 where treatment can only be administered +3 days of the targeted Day 1.

8.1.8.1 Timing of Dose Administration

8.1.8.1.1 Pembrolizumab/Placebo

Pembrolizumab/placebo treatments will begin on Day 1 of each cycle after all predose study procedures and assessments have been completed as detailed in the SoA.

Pembrolizumab will be administered as a fixed-dose of 200 mg using a 30-minute IV infusion Q3W. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (ie, infusion time is 30 minutes -5 min/+10 min).

8.1.8.1.2 Enzalutamide

Enzalutamide will be administered at a dose of 160 mg (four 40-mg capsules/tablets or two 80-mg tablets) orally QD. Enzalutamide treatment should begin on the same day as Cycle 1, Day 1 of pembrolizumab/placebo treatment, with the first dose administered after the end of the pembrolizumab/placebo IV infusion.

Subsequent enzalutamide treatments will be taken PO QD at approximately the same time each day on a continuous daily dosing schedule. Capsules/tablets can be taken with or without food. Capsules/tablets must be swallowed whole and should not be chewed, dissolved, or opened.

Participants must be instructed that if they miss a dose, or vomit at any time after taking a dose, they should take their next dose at its scheduled time. The site will validate compliance with study intervention (including missed or vomited doses) at each site visit according to

their standard operating procedure. If doses are missed or vomited, this must be indicated in the source documents and CRFs.

8.1.8.1.3 ADT

All participants will receive and remain on a stable regimen of ADT (LHRH agonist or antagonist) or have surgical castration. Dose and frequency of administration will be consistent with local product label and should not change during the study.

8.1.9 Discontinuation and Withdrawal

Participants who discontinue study intervention prior to completion of the treatment period should be encouraged to continue to be followed for all remaining study visits as outlined in the SoA and Section 8.10.3.

When a participant withdraws from participation in the study all applicable activities scheduled for the final study visit should be performed (at the time of withdrawal). Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

8.1.10 Participant Blinding/Unblinding

As of IA1, the study was unblinded. The subsections below are retained for reference.

STUDY INTERVENTION IDENTIFICATION INFORMATION IS TO BE UNBLINDED ONLY IF NECESSARY FOR THE WELFARE OF THE PARTICIPANT. EVERY EFFORT SHOULD BE MADE NOT TO UNBLIND.

For emergency situations where the investigator or medically qualified designee (consistent with local requirements) needs to identify the intervention used by a participant and/or the dosage administered, the investigator will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or medically qualified designee, the emergency unblinding call center will provide the information to them promptly and report unblinding to the Sponsor. Prior to contacting the emergency unblinding call center to request unblinding of a participant's intervention assignment, the investigator who is a qualified physician should make reasonable attempts to enter the toxicity grade of the AEs observed, the relation to study drug, the reason thereof, etc, in the medical chart. If it is not possible to record this assessment in the chart prior to the unblinding, the unblinding should not be delayed.

In the event that unblinding has occurred, the circumstances around the unblinding (eg, date, reason, and person performing the unblinding) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible.

Once an emergency unblinding has taken place, the principal investigator, site personnel, and Sponsor personnel may be unblinded so that the appropriate follow-up medical care can be provided to the participant.

Participants whose treatment assignment has been unblinded by the investigator or medically qualified designee and/or nonstudy treating physician must be discontinued from study intervention but should continue to be monitored in the study.

8.1.10.1 Non-emergency Unblinding

In the event of PD, there may be a need to unblind the participant's treatment assignment prior to initiating Second Course Treatment (Section 8.10.2.3). In this circumstance, unblinding to pembrolizumab versus placebo administration may occur on an individual basis and only after consultation with the Sponsor Clinical Director. Every effort should be made not to unblind the participant unless necessary.

8.1.11 Calibration of Equipment

The investigator or qualified designee has the responsibility to ensure that any device or instrument used for a clinical evaluation/test during a clinical study that provides information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and/or maintained to ensure that the data obtained are reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the study site.

8.2 Efficacy/Immunogenicity Assessments

8.2.1 Tumor Imaging and Assessment of Disease

As of Amendment 04: Central tumor response assessments will be discontinued. Imaging scans will no longer be submitted to iCRO nor read by BICR. Local tumor imaging should continue per SOC schedule for participants still on study treatment. The subsections below are retained for reference.

The process for image collection and transmission to the central imaging vendor can be found in the SIM. Tumor imaging is as follows:

- Chest, abdomen, and pelvis scans are required for all participants at Screening and on study. CT with IV and oral contrast is preferred or non-contrast CT of the chest and MRI of the abdomen and pelvis with IV gadolinium for participants in whom iodinated contrast is contraindicated, or when mandated by local practice.
- Bone scan (bone scintigraphy, radionuclide bone scan, etc.) of the whole body is required for all participants at Screening and on study for all scheduled imaging visits.
  - Other bone imaging modalities (ie, FDG-PET, PSMA PET, MRI, SPECT, etc.) cannot be a substitute for the bone scan (Appendix 8, Section 10.8.1).
- Brain imaging is only as clinically indicated at baseline and on study. MRI (strongly preferred) or CT with contrast of the brain.
- Additional imaging acquired as per standard of care or as clinically indicated, used to support radiographic disease progression or efficacy assessments, should be sent to the iCRO.

The same imaging technique regarding modality, ideally the same scanner, and the use of contrast should be used in a participant throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the assessment of response or progression based on imaging.

> **Note:** For the purposes of assessing tumor imaging, the term "investigator" refers to the local investigator at the site and/or the radiological reviewer at the site or at an offsite facility.

At Screening, participant eligibility will require radiographic documentation using local assessment (investigator assessment) that is verified by the BICR. When the investigator identifies baseline metastatic disease, the central imaging vendor will perform an expedited verification of eligibility that the participant's imaging shows at least 2 bone lesions on bone scan and/or visceral disease (eg, lung or liver) by CT/MRI per PCWG-modified RECIST 1.1 and will communicate the results to the study site and sponsor which is required prior to participant randomization. Participants whose metastatic disease is limited to lymph nodes are not eligible.

Upon investigator-assessed disease progression, the indicative scans are to be submitted immediately to iCRO for BICR verification of progression. After submission of scans, the iCRO will email the assessment to the site and Sponsor.

- If disease progression is not verified, the process continues as follows: If participant is clinically stable, continue study intervention per protocol
  - Resume imaging per protocol schedule
  - Send scans to iCRO
  - Continue local assessment
  - Do not change investigator assessment of progression
  - If subsequent scan(s) indicate progression, submit scans to iCRO to request verification
- If the participant is not clinically stable, best medical practice is to be applied

Before stopping study intervention or imaging or starting new anticancer therapy in a participant who is clinically stable, communication with the Sponsor is required.

If disease progression is verified, the process continues as follows:

- Investigator judgment will determine action
- If the participant is clinically stable and study intervention is to continue, communication with the Sponsor is required and a consent addendum must be signed

  Note: the consent addendum must be signed prior to starting study intervention after verification of disease progression is provided by the iCRO.
- Obtain scans locally per original protocol schedule

- Do not send scans to iCRO
- For the purpose of this decision process, lack of clinical stability is defined as:
  - Unacceptable toxicity
  - Clinical signs or symptoms indicating clinically significant disease progression
  - Decline in performance status
  - Rapid disease progression or threat to vital organs or critical anatomical sites (eg, CNS metastasis, respiratory failure due to tumor compression, spinal cord compression) requiring urgent alternative medical intervention.

The primary measure used by BICR for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status (eg, discontinuation of study intervention) will be PCWG-modified RECIST 1.1. PCWG PDu is not considered radiographic PD.

Assessment of treatment response in the soft tissues will be according to soft tissue rules of PCWG-modified RECIST 1.1, modified to follow a maximum of 10 target soft tissue lesions and a maximum of 5 target lesions per organ. Assessment of treatment response in bone will be according to the bone lesion rules of PCWG-modified RECIST 1.1, as described in Appendix 8.

Soft tissue and bone response assessments will be combined to produce an overall radiographic response, as follows:

Soft Tissue Response	Bone Scan Result	PCWG-modified RECIST 1.1 Time Point Response Entered Into CRF
PD	Any	PD
Any	PD	PD
Any (except PD)	PDu	PDu
NE	Non-PD, NED or NE	NE
NED	NE	NE
NED	Non-PD	Non-CR/Non-PD
NED	NED	NED
SD	Non-PD, NED, or NE*	SD
Non-CR/Non-PD	Non-PD, NED, or NE*	Non-CR/Non-PD
PR	Non-PD, NED or NE*	PR
CR	Non-PD or NE*	PR (if target lesions were present at baseline)
		Non-CR/Non-PD (if no target lesions at baseline)
CR	NED	CR

Abbreviations: CR complete response; CRF case report form; NE non evaluable; NED no evidence of disease; PCWG Prostate Cancer Working Group; PD progressive disease; PDu progressive disease unconfirmed; PR partial response; RECIST 1.1 Response Evaluation Criteria in Solid Tumors Version 1.1.

* If the bone scan is entirely missing or was not done, and bone lesions were present at baseline, then the overall response is non evaluable.

8.2.1.1 Initial Tumor Imaging

Initial tumor imaging at Screening must be performed within 42 days prior to the date of randomization. Tumor imaging by CT (or MRI) and radionuclide bone scan is required at Screening.

Scans performed as part of routine clinical management are acceptable for use as the screening scans if they are of diagnostic quality and performed within 42 days prior to the date of randomization. Scans are required to be sent to the central imagining vendor and verified for eligibility prior to randomization.

At Screening, all soft tissue lesions seen by CT (or MRI) and all bone lesions seen by radionuclide bone scan will be documented. In determining response to treatment or progression, investigators must evaluate all target and non-target lesions and search for new lesions at each imaging time point.

8.2.1.2 Tumor Imaging During the Study

On study imaging assessments must be performed every 12 weeks (84 days ± 7 days) from the date of randomization. All supplemental imaging must be submitted to the central imaging vendor.

Timing of imaging should follow calendar days from date of randomization and should not be adjusted for delays in cycle starts. Response must be confirmed at least 4 weeks later to be considered for best overall response.

Radiographic progression will be determined according to PCWG-modified RECIST 1.1. Disease progression in bone lesions should be confirmed by another bone scan ≥6 weeks after site assessed first radiographic evidence of disease progression.

8.2.1.3 End-of-Treatment and Follow-up Tumor Imaging

For participants who discontinue study intervention, tumor imaging should be performed at the time of treatment discontinuation (±4 week window). If previous imaging was obtained within 4 weeks prior to the date of discontinuation, then imaging at treatment discontinuation is not mandatory. For participants who discontinue study intervention due to BICR-verified disease progression, this is the final required tumor imaging.

If participants discontinue study intervention without documented disease progression, every effort is to be made to monitor disease status by acquiring tumor scans using the same schedule (every 12 weeks) calculated from the date of randomization (see Section 8.2.1.2).

Scans are to be continued until one of the following conditions are met:

- disease progression as defined by PCWG Modified RECIST 1.1 verified by BICR
- the start of a new anticancer treatment
- death
- withdrawal of consent
- the end of the study

8.2.1.4 Second Course (Retreatment) Tumor Imaging

Tumor imaging must be performed within 28 days prior to restarting treatment with pembrolizumab. Local reading (investigator assessment with site radiology reading) will be used to determine eligibility.

Response assessments and progressive disease are determined by investigator assessment.

The only Second Course scan to be provided to the iCRO is the baseline scan if it is the final scan for the Initial Treatment Phase or Extension First Course.

The first on-study imaging assessment should be performed at 12 weeks (84 days ±7 days) after the restart of treatment. Subsequent tumor imaging should be performed every 12 weeks (84 days ±7 days) or more frequently, if clinically indicated.

For participants who discontinue Second Course study intervention, tumor imaging should be performed at the time of intervention discontinuation (±4 week window). If previous imaging was obtained within 4 weeks prior to the date of discontinuation, then imaging at intervention discontinuation is not mandatory. For participants who discontinue study intervention due to documented disease progression, this is the final required tumor imaging.

For participants who discontinue Second Course study intervention without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging every 12 weeks (84 days ±7 days) until either the start of a new anticancer treatment, disease progression, death, or the end of the study, whichever occurs first.

8.2.1.5 Symptomatic Skeletal-Related Event (SSRE) Assessment

As of Amendment 04: SSRE assessments will be discontinued. The section below is retained for reference.

Participants will be assessed for SSRE as detailed in the SoA (Section 1.3). Time from randomization to first SSRE is defined by any of the following or a combination:

- Use of EBRT to prevent or relieve skeletal symptoms.
- Occurrence of new symptomatic pathologic bone fracture (vertebral or non-vertebral). Radiologic documentation is required.
- Occurrence of spinal cord compression. Radiologic documentation is required.
- Or tumor-related orthopedic surgical intervention, whichever occurs first.

Participants with new symptomatic pathological bone fractures and spinal cord compression will require radiologic documentation. Imaging modality used to assess the SSRE is at the discretion of the Investigator. All SSRE-related imaging should be submitted to the iCRO for quality control, storage, and possible retrospective review.

8.2.2 Prostate-specific Antigen Assessments

As of Amendment 04: Prostate-specific antigen assessments will be discontinued. The section below is retained for reference.

Central laboratory PSA assessment must occur according to the SoA (Section 1.3 SoA tables). PSA timing should follow calendar days and should not be adjusted for delays in cycle starts.

In participants who discontinue study intervention without BICR-verified disease progression, every effort should be made to continue monitoring their disease status by PSA

assessments until: 1) the start of new anticancer treatment, 2) radiographic disease progression, 3) death or 4) the end of the study, whichever occurs first. In these participants, PSA will be measured by a central laboratory.

Sample collection, storage, and shipment instructions will be in the Procedures Manual. The window for PSA collections is ±7 days.

8.2.3 Tumor Tissue Collection

Participants must provide a tumor tissue from a newly obtained core or excisional biopsy (obtained within 12 months of Screening) from soft tissue not previously irradiated (samples from tumors progressing in a prior site of radiation are allowed; other exceptions may be considered after Sponsor consultation). Participants with bone only or bone predominant disease may provide a bone biopsy sample (decalcification not allowed). However, if obtaining a new biopsy is not feasible, then participants may provide an archival tumor tissue sample after Sponsor consultation. FFPE tissue blocks are preferred to slides. Newly obtained biopsies are preferred to archive tissue.

Adequacy of these specimens for PD-L1 biomarker analysis will be required by a central laboratory prior to randomization.

8.2.4 Patient-reported Outcomes and Quality of Life Assessments

As of Amendment 04: PROs and Quality of Life assessments will be discontinued. The subsections below are retained for reference.

The BPI-SF, FACT-P, and EQ-5D-5L questionnaires should be administered at the site per the SoA in Section 1.3. Participants must complete the PRO questionnaires in the following order: BPI-SF, FACT-P, EQ-5D-5L.

It is best practice and strongly recommended that ePROs are administered to randomized participants prior to drug administration, AE evaluation, and disease status notification. If the participant does not complete the ePROs at a scheduled time point, the MISS_MODE form must be completed to capture the reason the assessment was not performed.

Site staff must not read, administer or complete the PRO questionnaires on behalf of the participant. If the participant is unable to read the questionnaire (eg, is blind or illiterate), that participant may still participate in the study, but is exempt from completing PRO questionnaires. Participants exempt in this regard should be flagged appropriately by the site staff.

8.2.4.1 BPI-SF

The BPI-SF is provided on an ePRO device at the site and will be completed by the participant at the time points specified in the SoA (Section 1.3).

The BPI-SF has 15 items that are rated on a 0 to 10 numeric rating scale, with 0 No Pain and 10 Worst Pain Imaginable. This instrument consists of 2 domains: pain severity and pain

interference. The pain severity domain consists of 4 items (Items #3, #4, #5, and #6), which assess pain at its "worst," "least," "average," and "now" (current pain) respectively on the 11-point scale. These 4 items may be averaged as a composite pain severity score or they may be interpreted individually [Dworkin, R. H., et al 2005] [Dworkin, R. H., et al 2008] [Dworkin, R. H., et al 2005] [Dworkin, R. H., et al 2008] [Food and Drug Administration 2009b]. In this study, the "worst pain" (Item #3) will be used as a single item in assessing pain progression. A composite pain severity score from all the 4 items will also be evaluated as 'pain severity progression'. A ≥2-point change in the average pain severity or in "worst pain" item is considered clinically meaningful.

The pain interference domain score is a mean of 7 items: general activity (Item #9A), mood (Item #9B), walking ability (Item #9C), normal work (Item #9D), relations with other people (Item #9E), sleep (Item #9F), and enjoyment of life (Item #9G), each scored on an 11-point scale from 0 (Does not interfere) to 10 (Completely interferes). Based on the BPI-SF scoring manual [Cleeland, C. S. 2009a], the following items are not used in scoring pain severity or pain interference domains: Items #1, #2, #7, and #8. Item #2 (a body map diagram) will not be included in the ePRO version of the BPI-SF. Item #7 (a free text field) describing pain medication use and Item #8, assessing amount of relief from pain treatments or medications provided in Item #7, will also not be included in the ePRO version of the BPI-SF. Analgesic use will be captured in a separate CRF.

8.2.4.2 FACT-P

FACT-P was developed as a disease-specific adjunct to the FACT measurement system and consists of FACT-G (general) which contains a 27-item self-report questionnaire measuring general health-related quality of life in 4 domains (physical, social, emotional, and functional well-being) and 12 prostate cancer-specific items. FACT-P (version 4) is self administered and requires approximately 8 to 10 minutes to complete.

8.2.4.3 EQ-5D-5L

The 5 health state dimensions in the EQ-5D-5L include the following: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is rated on a 5-point scale from 1 (no problem) to 5 (unable to/extreme problems). The EQ-5D-5L also includes a graded (0 to 100) VAS on which the participant rates his or her general state of health at the time of the assessment.

It is best practice and strongly recommended that ePROs are administered to randomized participants prior to drug administration, AE evaluation, and disease status notification. If the participant does not complete the ePROs at a scheduled time point, the MISS□MODE form must be completed to capture the reason the assessment was not performed.

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided.

Planned time points for all safety assessments are provided in the SoA.

8.3.1 Physical Examinations

The investigator or qualified designee will perform a complete physical exam during the Screening period. Clinically significant abnormal findings should be recorded as medical history. The time points for full physical exams are described in Section 1.3. After the first dose of study intervention, new clinically significant abnormal findings should be recorded as AEs.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.1.1 Full Physical Examination

The investigator or qualified designee will perform a complete physical exam during the Screening period. Clinically significant abnormal findings should be recorded as medical history. The time points for full physical exams are described in Section 1.3. After the first dose of study intervention, new clinically significant abnormal findings should be recorded as AEs.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.1.2 Directed Physical Examination

For cycles that do not require a full physical exam as defined in Section 1.3, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to study intervention administration. New clinically significant abnormal findings should be recorded as AEs.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.2 Vital Signs

Vital signs will be measured in a sitting, semi-recumbent or supine position after 5 minutes rest and will include weight, temperature, systolic and diastolic blood pressure, heart, and respiratory rate. Record vital signs prior to study intervention administration at treatment visits. Height will be measured at Screening only.

8.3.3 Electrocardiograms

A standard 12-lead ECG will be performed once at the Screening Visit using local standard procedures. Clinically significant abnormal findings should be recorded as medical history.

8.3.4 Clinical Safety Laboratory Assessments

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.
- If laboratory values from nonprotocol-specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).
- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

Details regarding specific laboratory procedures/assessments to be performed in this study are provided below. The total amount of blood/tissue to be drawn/collected over the course of the study (from prestudy to poststudy visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant can be found in the Study Procedures Manual. Refer to the Section 1.3 for the timing of laboratory assessments.

8.3.4.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry, and urinalysis are specified in Appendix 2.

8.3.5 Performance Assessments

8.3.5.1 Eastern Cooperative Oncology Group Performance Scale

The investigator or qualified designee will assess ECOG status (see Appendix 11) at Screening and prior to the administration of each dose of study intervention as specified in the SoA (Section 1.3).

8.4 Adverse Events, Serious Adverse Events, and Other Reportable Safety Events

The definitions of an AE or SAE, as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE, and other reportable safety event reports can be found in Appendix 3.

Adverse events, SAEs, and other reportable safety events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators need to document if an SAE was associated with a medication error, misuse, or abuse.

Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome according to Section 8.4.3. The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity, and causality.

8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information

All AEs, SAEs, and other reportable safety events that occur after the informed consent form is signed, but before intervention randomization, must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event cause the participant to be excluded from the study, or is the result of a protocol-specified intervention, including, but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

- All AEs from the time of intervention randomization through 30 days following cessation of study intervention must be reported by the investigator.
- All AEs meeting serious criteria, from the time of intervention allocation/randomization through 90 days following cessation of study intervention or 30 days following cessation of study intervention if the participant initiates new anticancer therapy, whichever is earlier, must be reported by the investigator.
- All pregnancies and exposure during breastfeeding of participant's female partner, from the time of intervention randomization through 120 days following cessation of study intervention, or 30 days following cessation of study intervention if the participant initiates new anticancer therapy must be reported by the investigator.
- Additionally, any SAE brought to the attention of an investigator at any time outside the time period specified above must be reported immediately to the Sponsor if the event is considered related to study intervention.

Investigators are not obligated to actively seek AEs or SAEs or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and the investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 9.

Table 9 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Period:** Consent to Randomization/ Allocation	**Reporting Period:** Randomization/ Allocation Through Protocol-specified Follow-up Period	**Reporting Period:** After the Protocol-specified Follow-up Period	Time Frame to Report Event and Follow-up Information to Sponsor
NSAE	Report if: – due to protocol-specified intervention – causes exclusion – participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
SAE	Report if: – due to protocol-specified intervention – causes exclusion – participant is receiving placebo run-in or other run-in treatment	Report all	Report if: – drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event
Pregnancy/Lactation Exposure	Report if: – participant has been exposed to any protocol-specified intervention (eg, procedure, washout, or run-in treatment including placebo run-in) Exception: A positive pregnancy test at the time of initial screening is not a reportable event.	Report all	Previously reported – Follow to completion/ termination; report outcome	Within 24 hours of learning of event
ECI (require regulatory reporting)	Report if: – due to intervention – causes exclusion	Report – potential DILI – require regulatory reporting	Not required	Within 24 hours of learning of event
ECI (do not require regulatory reporting)	Report if: – due to intervention – causes exclusion	Report – non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event

DILI drug induced liver injury; ECI event of clinical interest; NSAE nonserious adverse event; SAE serious adverse event.

8.4.2 Method of Detecting AEs, SAEs, and Other Reportable Safety Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs and other reportable safety events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.4.3 Follow-up of AE, SAE, and Other Reportable Safety Event Information

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and other reportable safety events, including pregnancy and exposure during breastfeeding of participant's female partner, ECIs, cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAE

Prompt notification (within 24 hours) by the investigator to the Sponsor of SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements and global laws and regulations relating to safety reporting to regulatory authorities, IRB/IECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAE) from the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding in a participant's female partner (spontaneously reported to the investigator or their designee), that occurs during the study are reportable to the Sponsor.

All reported pregnancies of participant's female partner must be followed to the completion/termination of the pregnancy.

Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as

serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

8.4.6 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

Efficacy endpoints as outlined in this section will not be reported to the Sponsor as described in Section 8.4.1.

Specifically, the suspected/actual events covered in this exception include any event that is disease progression of the cancer under study.

The Sponsor will monitor unblinded aggregated efficacy endpoint events and safety data to ensure the safety of the participants in the study.

Any suspected endpoint that upon review is not progression of the cancer under study will be forwarded to Global Pharmacovigilance as an SAE within 24 hours of determination that the event is not progression of the cancer under study.

8.4.7 Events of Clinical Interest

Selected nonserious and SAEs are also known as ECIs and must be reported to the Sponsor.

Events of clinical interest for this study include:

1. An overdose of Sponsor's product, as defined in Section 8.5, that is not associated with clinical symptoms or abnormal laboratory results.
2. An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

   *Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The study site guidance for assessment and follow up of these criteria can be found in the Investigator Study File Binder (or equivalent).

8.5 Treatment of Overdose

For this study, an overdose of pembrolizumab will be defined as any dose of 1000 mg or greater (>5 times the indicated dose).

No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

An enzalutamide overdose is defined as at least 2 daily doses of study intervention taken the same calendar day. In the event of an overdose, treatment with study drug should be interrupted and general supportive measures initiated, taking into consideration the half-life is 5.8 days for enzalutamide. Participants may be at increased risk of seizures following an overdose of enzalutamide. Neither the effects of overdose of enzalutamide nor an antidote to overdose are known.

The medical monitor must be contacted in the event of a study drug overdose.

8.6 Pharmacokinetics

PK parameters will not be evaluated in this study.

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

CCI

CCI

[redacted]

8.10 Visit Requirements

Visit requirements are outlined in Section 1.3. Specific procedure-related details are provided in Section 8.

8.10.1 Screening

Written consent must be obtained prior to performing any protocol-specific procedure. Results of a test performed prior to the participant signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame.

Screening procedures are to be completed within 42 days prior to the first dose of study intervention. except for the following:

- Laboratory tests are to be performed within 10 days prior to the first dose of study intervention. An exception is HIV and hepatitis testing which may be done up to 42 days prior to the first dose of randomization if required by local regulations.
- Evaluation of ECOG is to be performed within 10 days prior to the first dose of study intervention.
- Tumor tissue from a newly obtained core or excisional biopsy obtained within 12 months of Screening. Archival tumor tissue sample (>12 months) can be submitted after Sponsor consultation.

Participants may be rescreened up to two times after initially failing to meet the inclusion/exclusion criteria. Results from assessments during the initial screening period are acceptable in lieu of a repeat screening test if performed within the specified time frame and the corresponding inclusion/exclusion criteria is met. Participants who are rescreened will retain their original screening number.

8.10.2 Treatment Period

Visit requirements are outlined in the SoA (Section 1.3). Specific procedure-related details are provided in Section 8.1.

8.10.2.1 Extension First Course

If pembrolizumab/placebo is completed or discontinued for reasons other than progressive disease, participants still receiving enzalutamide will continue to receive enzalutamide + ADT and transition into Extension First Course. For these participants, transitioning into Extension First Course will allow for less frequent clinic visits by increasing the cycle length to 84 days (Table 2). Transition into Extension First Course should occur within 21 days (± 7 days) of the last cycle received in the Initial Treatment Course. PSA and imaging assessments will continue per original calendar-based schedule calculated from randomization. Treatment with enzalutamide/ADT will then continue until criteria for discontinuation is met (eg, disease progression).

Post-treatment assessments listed in the SoA (Table 1) will not be required if participants transition into Extension First Course. Post-treatment visits will occur once all study medication (pembrolizumab/placebo/enzalutamide) is discontinued.

Specific procedures to be performed during Extension First Course, as well as their prescribed times and associated visit windows, are outlined in the SoA in Section 1.3.

8.10.2.2 End of Treatment Visit

The End of Treatment Visit should occur at the time study intervention is discontinued. If the End of Treatment Visit occurs 30 days after the last dose of study intervention, at the time of the mandatory Safety Follow-up Visit, procedures do not need to be repeated. Visit requirements are outlined in the SoA (Section 1.3). Specific procedure-related details are provided above in Section 8 Study Assessments and Procedures. Prior to discontinuing participants from therapy, submit the Treatment Termination & Disease Assessment Termination Form.

8.10.2.3 Second Course

NOTE: As of Amendment 04, Second Course treatment is not an option for participants. There are currently no participants in the Second Course Phase. The subsection below is retained for reference.

All participants who stop pembrolizumab with SD or better may be eligible for up to 17 additional cycles (approximately 1 year) of pembrolizumab treatment if they have BICR-verified progression after stopping study intervention from the Initial Treatment Phase. In this circumstance, unblinding to pembrolizumab versus placebo administration may occur on an individual basis and only after consultation with Sponsor Clinical Director as outlined in Section 8.1.10.1. Participants should continue treatment with ADT. Enzalutamide may be continued at the investigator's discretion during the Second Course treatment. This

retreatment is termed the Second Course Phase of this study and is only available if the study remains open and the participant meets the following conditions:

EITHER

- stopped initial pembrolizumab/placebo after attaining an investigator-determined confirmed CR based on PCWG-modified RECIST 1.1; and
- was treated with at least 8 cycles of pembrolizumab/placebo before discontinuing treatment; and
- received at least 2 treatments with pembrolizumab/placebo beyond the date when the initial CR was declared.

OR

- had SD, PR, or CR and stopped pembrolizumab/placebo after completion of 35 cycles (approximately 2 years) of pembrolizumab/placebo for reasons other than disease progression or intolerability

AND

- experienced BICR-verified radiographic disease progression per PCWG-modified RECIST 1.1 after stopping pembrolizumab/placebo; and
- upon unblinding at the time of centrally verified disease progression, were found to have received pembrolizumab (refer to Section 8.1.10); and
- no new anticancer treatment was administered after the last dose of study intervention; and
- demonstrate adequate organ function as detailed in Section 5.1; and
- does not have a history or current evidence of any condition, therapy, or laboratory abnormality that might interfere with the subject's participation for the full duration of the trial or is not in the best interest of the subject to participate, in the opinion of the treatment investigator; and
- the study is ongoing.

An objective response or disease progression that occurs during the Second Course Phase for a participant will not be counted as an event for the primary analysis of either endpoint in this study.

8.10.3 Post-treatment Visits

Post-treatment visits are outlined in each SoA specified in Section 1.3. Post-treatment assessments listed in the Initial Treatment Phase (Table 1) will not be required if participants transition into Extension First Course (Table 2). Post-treatment visits will occur once all

study medication (pembrolizumab/placebo and enzalutamide) is discontinued (ie, do not continue with enzalutamide in Extension First Course).

8.10.3.1 Safety Follow-up Visit

The mandatory Safety Follow-up Visit should be conducted approximately 30 days after the last dose of study intervention or before the initiation of a new anticancer treatment, whichever comes first.

Participants who are eligible for retreatment with pembrolizumab may have up to 2 Safety Follow-up Visits, 1 after the Initial/Extension Treatment Phase and 1 after the Second Course Treatment.

8.10.3.2 Follow-up Visits

As of Amendment 04: Follow-Up Visits will be discontinued. This section below is retained for reference.

Participants who discontinue all study intervention (pembrolizumab/placebo and enzalutamide) for a reason other than BICR-verified radiographic disease progression will move into the Follow-up Phase. Follow-up visits will be scheduled every 12 weeks (84 days ± 7 days). For participants who discontinue study intervention without documented BICR-verified disease progression, every effort should be made to continue monitoring disease status by PSA and radiologic imaging (CT/MRI and bone scans) using the same imaging schedule used while on treatment (every 12 weeks) calculated from the date of randomization (see Section 8.2.1.2) until the start of a new anticancer treatment, BICR-verified disease progression, death, withdrawal of consent, or the end of the study, whichever occurs first (or if the participant begins retreatment with pembrolizumab as detailed in Section 8.10.2.3). Information regarding poststudy anticancer treatment will be collected if new treatment is initiated.

Participants who are eligible to receive retreatment with pembrolizumab according to the criteria in Section 8.10.2.3 will move from the Follow-up Phase to the Second Course Phase when they experience disease progression. Details are provided in the SoA (Section 1.3) for retreatment with pembrolizumab.

Prior to discontinuing participants from follow-up, submit the Treatment Termination & Disease Assessment Termination Form.

8.10.3.3 Survival Follow-up

As of Amendment 04: Survival Follow-up visit will be discontinued. Those participants remaining on study treatment at the time of Amendment 04, should continue to be monitored in the study through the AE reporting Period (section 8.4). The section below is retained for reference.

Participants who experience BICR-verified radiographic progression or start a new anticancer therapy, will move into the Survival Follow-up Phase and should be contacted by

telephone approximately every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

8.10.4 Survival Status

To ensure current and complete survival data is available at the time of database locks, updated survival status may be requested during the course of the study by the Sponsor. For example, updated survival status may be requested prior to but not limited to an eDMC review, interim and/or final analysis. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding participants that have a previously recorded death event in the collection tool).

9 STATISTICAL ANALYSIS PLAN

As of Amendment 04: The Statistical Analysis Plan is amended as follows.

NOTE: Based on the data from an interim safety and efficacy analysis for KEYNOTE-991 (data cutoff 31-OCT-2022), eDMC recommended stopping the study for futility because pembrolizumab in combination with enzalutamide and ADT did not demonstrate an improvement in OS or rPFS, the trial's dual primary endpoints, compared to placebo plus enzalutamide and ADT and appears unlikely to do so in a future analysis. Based upon these data and the recommendation of the eDMC, the study was unblinded (as of 19-JAN-2023). All the prespecified interim analyses after IA1 and final analysis of the study described in the SAP will not be performed. Safety analysis will be performed at the end of the study. There will be no further analyses for efficacy and ePRO endpoints collected from participants after IA1 cutoff date.

This section outlines the statistical analysis strategy and procedures for the study. The study has been unblinded as of 19-JAN-2023. Changes made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses that occurred prior to Amendment 04 were documented in previous protocol amendments (consistent with International Conference on Harmonisation [ICH] Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, but prior to unblinding/final data base lock, will be documented in a sSAP and referenced in the CSR for the study. Post hoc exploratory analyses will be clearly identified in the CSR. CCI [redacted]

9.1 Statistical Analysis Plan Summary

Key elements of the Statistical Analysis Plan are summarized below. The comprehensive plan is provided in Sections 9.2 through 9.12. **As of Amendment 04, all the prespecified interim analyses after IA1 and final analysis of the study described in the SAP will not be performed. Safety analysis will be performed at the end of the study; there will be no further analyses of efficacy and ePRO endpoints collected from participants after IA1 cutoff date. The SAP summary has been updated accordingly.**

Study Design Overview	A Phase 3, Randomized, Double-blind Trial of Pembrolizumab (MK-3475) Plus Enzalutamide Plus ADT Versus Placebo Plus Enzalutamide Plus ADT in Participants With Metastatic Hormone-Sensitive Prostate Cancer (mHSPC)
Treatment Assignment	Approximately 1232 eligible participants will be randomized in a 1:1 ratio to one of the following 2 treatment arms: • Arm 1: pembrolizumab plus enzalutamide plus ADT • Arm 2: placebo plus enzalutamide plus ADT Randomization stratification factors are: • Prior docetaxel for mHSPC: Yes vs No • High-volume disease: Yes vs No .
Analysis Populations	Efficacy: ITT Safety: APaT
Primary Endpoint(s)	1. rPFS 2. OS
Key Secondary Endpoints	1. TFST 3. TTSSRE
Statistical Methods for Key Efficacy Analyses	The primary hypotheses will be evaluated by comparing pembrolizumab plus enzalutamide plus ADT arm to placebo plus enzalutamide plus ADT arm with respect to rPFS, OS, TFST, and TTSSRE using a stratified log-rank test. The hazard ratio will be estimated using a Cox regression model. Event rates over time will be estimated within each treatment group using the Kaplan-Meier method.
Statistical Methods for Key Safety Analyses	The analysis of safety results will follow a tiered approach. The tiers differ with respect to the analyses that will be performed. There are no events of interest that warrant elevation to Tier 1 events in this study. Tier 2 parameters will be assessed via point estimates with 95% confidence interval (CIs) provided for between-group comparison; only point estimates by treatment group are provided for Tier 3 safety parameters. The 95% CIs for the between-treatment differences in percentages will be provided using the Miettinen & Nurminen method.

Interim Analyses	CCI [redacted]
Multiplicity	

Sample Size and Power	CCI [redacted]

9.2 Responsibility for Analyses/In-house Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the Sponsor.

This study will be conducted as a double-blind study under in-house blinding procedures. The official, final database will not be unblinded until medical/scientific review has been performed, protocol deviations have been identified, and data have been declared final and complete.

The Clinical Biostatistics department of the Sponsor will generate the randomized allocation schedule for study intervention assignment for this protocol, and the randomization will be implemented in an IRT by a study vendor.

Blinding procedure related to the planned interim analyses is described in Section 9.7.

Extension Portion in China:

For all participants in China, including participants randomized in the global portion and the extension portion, participant-level treatment randomization information will be blinded to the statistician(s)/programmer(s) responsible for the analysis of the Extension Portion in China until the extension portion database lock is achieved. The extent to which individuals are unblinded to the results will be limited. Blinded and unblinded members will be clearly documented.

9.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3.

9.4 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated for within- and between-treatment differences are listed below, followed by the descriptions of the derivations of selected endpoints.

9.4.1 Efficacy Endpoints

9.4.1.1 Primary

Radiographic Progression-free Survival PCWG-modified RECIST 1.1 by BICR is defined as the time from randomization to the first documented disease progression or death due to any cause, whichever occurs first.

Overall Survival is defined as the time from randomization to death due to any cause.

9.4.1.2 Key Secondary

TFST is defined as the time from randomization to initiation of the first subsequent anticancer therapy or death, whichever occurs first. Any systemic treatment for prostate cancer that is intended to prolong survival is included. Radiopharmaceutical therapy with the purpose of cancer treatment is also included, for example, but not limited to, Radium 223. Excluded from the definition are palliative treatments intended for supportive care only, eg, prednisone prescribed for pain, surgery for skeletal-related event such as cord compression or pathologic fracture, and localized radiotherapy for pain management only.

TTSSRE is defined as the time from randomization to the first symptomatic skeletal-related event, defined as:

- first use of EBRT to prevent or relieve skeletal symptoms,
- occurrence of new symptomatic pathologic bone fracture (vertebral or non-vertebral),
- occurrence of spinal cord compression,
- or tumor-related orthopedic surgical intervention,

whichever occurs first.

9.4.1.3 Secondary

PSA response rate is defined as the proportion of participants in the analysis population with PSA decline of ≥50% from baseline measured twice at least 3 weeks apart.

Objective response rate PCWG-modified RECIST 1.1 by BICR is defined as the proportion of participants in the analysis population who have a best overall response of either confirmed CR or PR.

Duration of response PCWG-modified RECIST 1.1 by BICR is defined as the time from the earliest date of first documented evidence of confirmed CR or PR until earliest date of disease progression or death from any cause, whichever occurs first.

Time to PSA progression is defined as the time from randomization to PSA progression. Participants without PSA progression will be censored at the last PSA assessment date. The PSA progression date is defined as the date that 1) ≥25% increase and ≥2 ng/mL above the nadir, and which is confirmed by a second value ≥3 weeks later if there is PSA decline from baseline 2) or ≥25% increase and ≥2 ng/mL increase from baseline beyond 12 weeks if there is no PSA decline from baseline.

PSA undetectable rate is defined as the proportion of participants in the analysis population with PSA <0.2 ng/mL during study intervention.

Time to radiographic soft tissue progression per soft tissue rule of PCWG-modified RECIST 1.1 by BICR is defined as the time from randomization to radiographic soft tissue progression.

PFS2 defined as the time from randomization to disease progression as determined by investigator assessment after next-line of therapy or death from any cause, whichever occurs first.

9.4.1.4 Exploratory

CCI [redacted]

9.4.2 Safety Endpoints

Safety measurements are described in Section 4.2.1.2.

Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse events, laboratory values and vital signs.

9.4.3 PRO Endpoints

9.4.3.1 Time to Pain Progression

Time to pain progression is defined as the time from randomization to the earliest date of pain progression based on the BPI-SF Item #3 "worst pain in 24 hours" and opiate use.

9.4.3.2 FACT-P

FACT-P was developed as a disease-specific adjunct to the FACT measurement system and consists of FACT-G (general) which contains a 27-item self-report questionnaire measuring general health-related quality of life in 4 domains (physical, social, emotional, and functional well-being) and 12 prostate cancer-specific items.

PRO endpoints related to FACT-P include

- The change from baseline at the latest time point when prespecified criteria are met with regards to PRO completion and compliance rates
- Proportion of participants with best score of "improved"
- Proportion of participants with best score of "worsened"
- Proportion of participants with best score of "no change"

for each of the following FACT-P scores/scales

- **FACT-P total score:** FACT-G score +prostate cancer subscore
- **FACT-G total score:** physical well-being + social/family well-being + emotional well-being + functional well-being
- **PCS:** prostate cancer subscore
- **PWB:** physical well-being
- **SWB:** social/family well-being
- **EWB:** emotional well-being
- **FWB:** functional well-being
- **TOI** (trial outcome index): physical well-being + functional well-being + prostate cancer subscore
- **FAPSI-6** (FACT advanced prostate symptom index 6): a symptom score made up of 6 items from within the FACT P (3 pain items, 1 fatigue item, 1 weight loss item, and 1 condition getting worse item)
- **PCS pain-related score:** Calculated from the four questions on pain in the FACT-P

A best response of "Improved", "No Change", and "Worsened", defined according to Table 10 and Table 11 will be calculated for each participant for each FACT-P score.

Table 10 Definition of Visit Response for FACT-P score

	Minimum important difference (MID)
FACT-P-Total	10
FACT-G Total	7
FAPSI-6	3
TOI	9
PCS	3
PCS pain-related score	2
FWB, PWB, SWB, EWB	3

Abbreviations: EWB emotional well being; FACT G Functional Assessment of Cancer Therapy General; FACT P Functional Assessment of Cancer Therapy Prostate Cancer; FAPSI 6 Functional Assessment of Prostate Cancer Symptoms Index 6; FWB functional well being; PCS Prostate Cancer Symptoms; PWB physical well being; SWB social/family well being; TOI Trial Outcome Index.

Table 11 Definition of Best Score for FACT-P score

Overall Score Response	**Criteria**
Improved	Two consecutive visit responses of "improved".
No change	Does not qualify for overall score response of "improved". Two consecutive visit responses of either "no change" or "improved" and "no change".
Worsened	Does not qualify for overall score response of "improved" or "no change". A visit response of "worsened".
Other	Does not qualify for 1 of the above.

9.4.3.3 BPI-SF

A validated questionnaire commonly used in cancer trials that includes several individual items measured on a scale of 0 to 10, with lower scores representing lower levels of pain intensity or less interference of pain with activities of daily living (eg, sleep, mood, and activity).

In addition to time to pain progression, PRO endpoints related to BPI-SF include but not limited to

- time to pain severity progression
- the change from baseline in pain interference at the latest time point when prespecified criteria are met with regards to PRO completion and compliance rates

Details of PRO endpoints will be provided in sSAP.

9.4.3.4 EQ-5D-5L

The 5 health state dimensions in the EQ-5D-5L include the following: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is rated on a 5-point scale from 1 (no problem) to 5 (unable to/extreme problems). The EQ-5D-5L also includes a graded (0 to 100) vertical visual analog scale on which the participant rates his or her general state of health at the time of the assessment.

PRO endpoints related to EQ-5D-5L include but are not limited to the change from baseline in EQ-5D-5L VAS at the latest time point when prespecified criteria are met with regards to PRO completion and compliance rates.

CCI

[redacted]

CCI [redacted]

9.6 Statistical Methods

NOTE: As of Amendment 04, all the prespecified interim analyses after IA1 and final analysis of the study described in the SAP will not be performed. Safety analysis will be performed at the end of the study; there will be no further analyses of efficacy and ePRO endpoints collected from participants beyond the IA1 cutoff date. The subsections below are retained for reference.

Statistical testing and inference for safety analyses are described in Section 9.6.2. CCI [redacted]. Nominal p-values may be computed for other efficacy analyses, but should be interpreted with caution due to potential issues of multiplicity, sample size, etc. Unless otherwise stated, all statistical tests will be conducted at the α 0.025 (1-sided) level. In the event that there are a small number of responses/events in one or more strata, for the purpose of analysis strata will be combined to ensure sufficient number of responses/events in each stratum. Details regarding the combining of strata will be specified in the sSAP prior to database lock based on a blinded review of response counts by stratum.

9.6.1 Statistical Methods for Efficacy Analyses

This section describes the statistical methods that address the primary and key secondary objectives. Methods related to other objectives will be described in the sSAP.

The efficacy analyses for ORR, DOR and rPFS will include responses and documented progression events that occur prior to Second Course Treatment.

9.6.1.1 Radiographic Progression-Free Survival

The non-parametric Kaplan-Meier method will be used to estimate the rPFS curve in each treatment group. The treatment difference in rPFS will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (ie, hazard ratio) between the treatment arms. The hazard ratio and its 95% confidence interval from the stratified Cox model with Efron's method of tie handling and with a single treatment covariate will be

reported. The stratification factors used for randomization will be applied to both the stratified log-rank test and the stratified Cox model.

CCI

CCI [redacted]

9.6.1.2 Overall Survival

The non-parametric Kaplan-Meier method will be used to estimate the survival curves. The treatment difference in survival will be assessed by the stratified log-rank test (based on the stratification factors defined in Section 6.3.2). A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (ie, the hazard ratio). The HR and its 95% CI from the stratified Cox model with a single treatment covariate will be reported. The stratification factors used for randomization (Section 6.3.2) will be applied to both the stratified log-rank test and the stratified Cox model. Participants without documented death at the time of analysis will be censored at the date of last known to be alive. CCI [redacted]

CCI [redacted]

9.6.1.3 Time to Initiation of the First Subsequent Anticancer Therapy (TFST)

The non-parametric Kaplan-Meier method will be used to estimate the TFST curve in each treatment group. The treatment difference in TFST will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (ie, hazard ratio) between the treatment arms. The hazard ratio and its 95% confidence interval from the stratified Cox model with Efron's method of tie handling and with a single treatment covariate will be reported. The stratification factors used for randomization will be applied to both the stratified log-rank test and the stratified Cox model. Participants without documented event at the time of analysis will be censored at the date of last known time to have not received subsequent new anticancer therapy.

9.6.1.4 Time to Symptomatic Skeletal-Related Event (TTSSRE)

The non-parametric Kaplan-Meier method will be used to estimate the TTSSRE curve in each treatment group. The treatment difference in TTSSRE will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (ie, hazard ratio) between the treatment arms. The hazard ratio and its 95% confidence interval from the stratified Cox model with Efron's method of tie handling and with a single treatment covariate will be reported. The stratification factors used for randomization will be applied to both the stratified log-rank test and the stratified Cox model. Participants without documented event at the time of analysis will be censored at the date of last known time to be free of symptomatic skeletal-related event.

Details of efficacy analyses for other endpoints will be provided in the sSAP.

9.6.1.5 Analysis Strategy for Key Efficacy Endpoints

Table 13 summarizes the primary analysis approach for key efficacy endpoints.

Table 13 Efficacy Analysis Methods for Key Efficacy Endpoints

Endpoint/Variable	Statistical Method[a]	Analysis Population	Missing Data Approach
Primary Analysis:			
rPFS per PCWG-modified RECIST 1.1 as assessed by BICR	Testing: Stratified log-rank Test Estimation: Stratified Cox model with Efron's tie handling method.	ITT	Censored according to rules in Table 12
OS	Testing: Stratified log-rank Test Estimation: Stratified Cox model with Efron's tie handling method.	ITT	Censored at last known alive date
Key Secondary Analysis :			
TFST	Testing: Stratified Log-rank Test Estimation: Stratified Cox model with Efron's tie handling method.	ITT	Censored at the last known time to have not received subsequent new anticancer therapy
TTSSRE	Testing: Stratified Log-rank Test Estimation: Stratified Cox model with Efron's tie handling method.	ITT	Censored at the last known time to be free of symptomatic skeletal-related event

Abbreviations: BICR blinded independent central review; ITT intention to treat; OS overall survival; PCWG Prostate Cancer Working Group; modified RECIST 1.1 modified Response Evaluation Criteria in Solid Tumors Version 1.1; rPFS radiographic progression free survival; TFST time to initiation of the first subsequent anticancer therapy or death; TTSSRE time to symptomatic skeletal related event

a. Statistical models are described in further detail in the text. For stratified analyses, the stratification factors used for randomization will be applied to the analysis. Small strata will be combined in a way specified by a blinded statistician prior to the analysis.

CCI

[redacted]

9.6.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse experiences, laboratory tests, vital signs, and ECG measurements.

The analysis of safety results will follow a tiered approach (Table 14). The tiers differ with respect to the analyses that will be performed. Adverse experiences (specific terms as well as system organ class terms) and events that meet predefined limits of change in laboratory and vital signs, and ECG parameters are either prespecified as Tier-1 endpoints or will be classified as belonging to "Tier 2" or "Tier 3," based on observed proportions of participants with an event.

Tier 1 Events

Safety parameters or AEs of special interest that are identified a priori constitute Tier 1 safety endpoints that will be subject to inferential testing for statistical significance.

AEs that are immune mediated or potentially immune mediated are well documented and will be evaluated separately; however, these events have been characterized consistently throughout the pembrolizumab clinical development program and determination of statistical significance is not expected to add value to the safety evaluation. The combination of pembrolizumab and enzalutamide has not been associated with any new safety signals. Finally, there are no known AEs associated with participants with prostate cancer for which determination of a p value is expected to impact the safety assessment. Therefore, there are no Tier 1 events for this protocol.

Tier 2 Events

Tier 2 parameters will be assessed via point estimates with 95% confidence intervals provided for between-treatment differences in the proportion of participants with events using the Miettinen and Nurminen method, an unconditional, asymptotic method [Miettinen, O. and Nurminen, M. 1985].

Membership in Tier 2 requires that at least [redacted] of participants in any treatment group exhibit the event; all other AEs and predefined limits of change will belong to Tier 3. The threshold of at least [redacted] of participants was chosen for Tier 2 events because the population enrolled in this study are in critical conditions and usually experience various AEs of similar types regardless of treatment; events reported less frequently than [redacted] of participants would obscure the assessment of the overall safety profile and add little to the interpretation of potentially meaningful treatment differences. In addition, Grade 3 to 5 AEs [redacted] and SAEs [redacted] will be considered Tier 2 endpoints. Because many 95% CIs may be provided without adjustment for multiplicity, the CIs should be regarded as a helpful descriptive measure to be used in safety review, not a formal method for assessing the statistical significance of the between-group differences.

Tier 3 Events

Safety endpoints that are not Tier 1 or 2 events are considered Tier 3 events. Only point estimates by treatment group are provided for Tier 3 safety parameters.

Continuous Safety Measures

For continuous measures such as changes from baseline in laboratory, vital signs, and ECG parameters, summary statistics for baseline, on treatment, and change from baseline values will be provided by treatment group in table format.

Table 14 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint	95% CI for Treatment Comparison	Descriptive Statistics
Tier 2	Any AE [redacted]	X	X
	Any Grade 3 to 5 AE [redacted]	X	X
	Any serious AE [redacted]	X	X
Tier 3	Any AE		X
	Change from baseline results (laboratory test toxicity grade, vital signs, ECGs)		X

Abbreviations: AE adverse event; CI confidence interval; ECG electrocardiogram; X results will be provided.

9.6.3 Analysis Methods for PRO Endpoints

Time to pain progression (TTPP)

For TTPP, the Kaplan-Meier method will be used to estimate the survival curves for TTPP, separately, in each treatment arm. In addition, corresponding survival curves will be estimated by treatment arm. Stratified Cox proportional hazards models with Efron's method of tie handling will be used to assess the magnitude of the treatment difference. Stratification factors used for randomization will be used in the stratified Cox proportional hazards models. The hazard ratio, 95% CI, and nominal p-value will be reported. Details of additional PRO analyses will be included in the sSAP.

9.6.4 Demographic and Baseline Characteristics

The comparability of the treatment groups for each relevant demographic and baseline characteristic will be assessed by the use of tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of participants screened and randomized and the primary reason for screening failure and discontinuation will be displayed. Demographic variables, baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables.

9.7 Interim Analyses

[redacted]

CCI

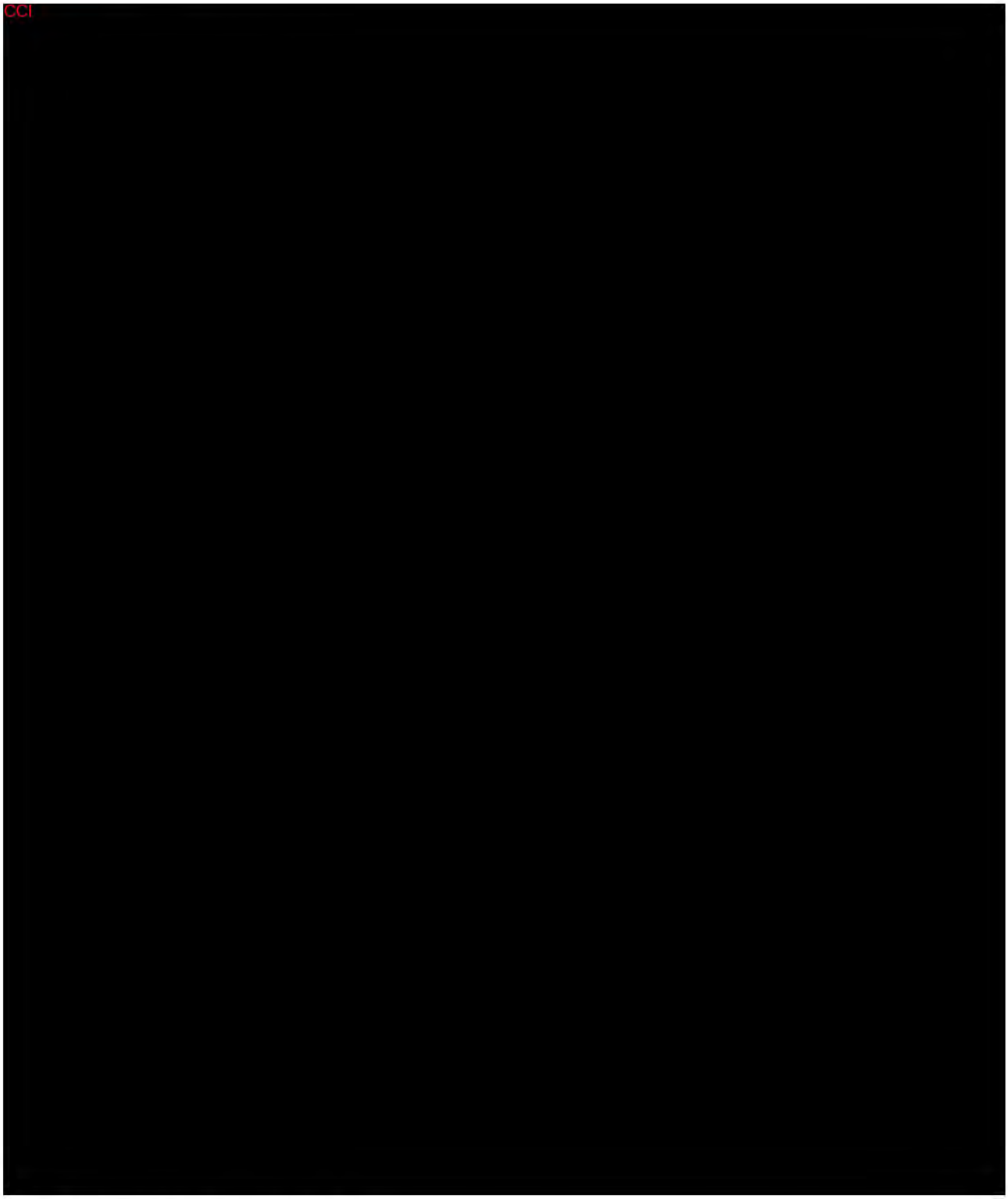
[redacted]

9.7.1 Efficacy Interim Analyses

CCI

[redacted]

CCI



9.7.2 Safety Interim Analyses

The eDMC conducted regular safety interim analyses. The timing of these safety interim analyses was specified in the eDMC charter.

9.8 Multiplicity

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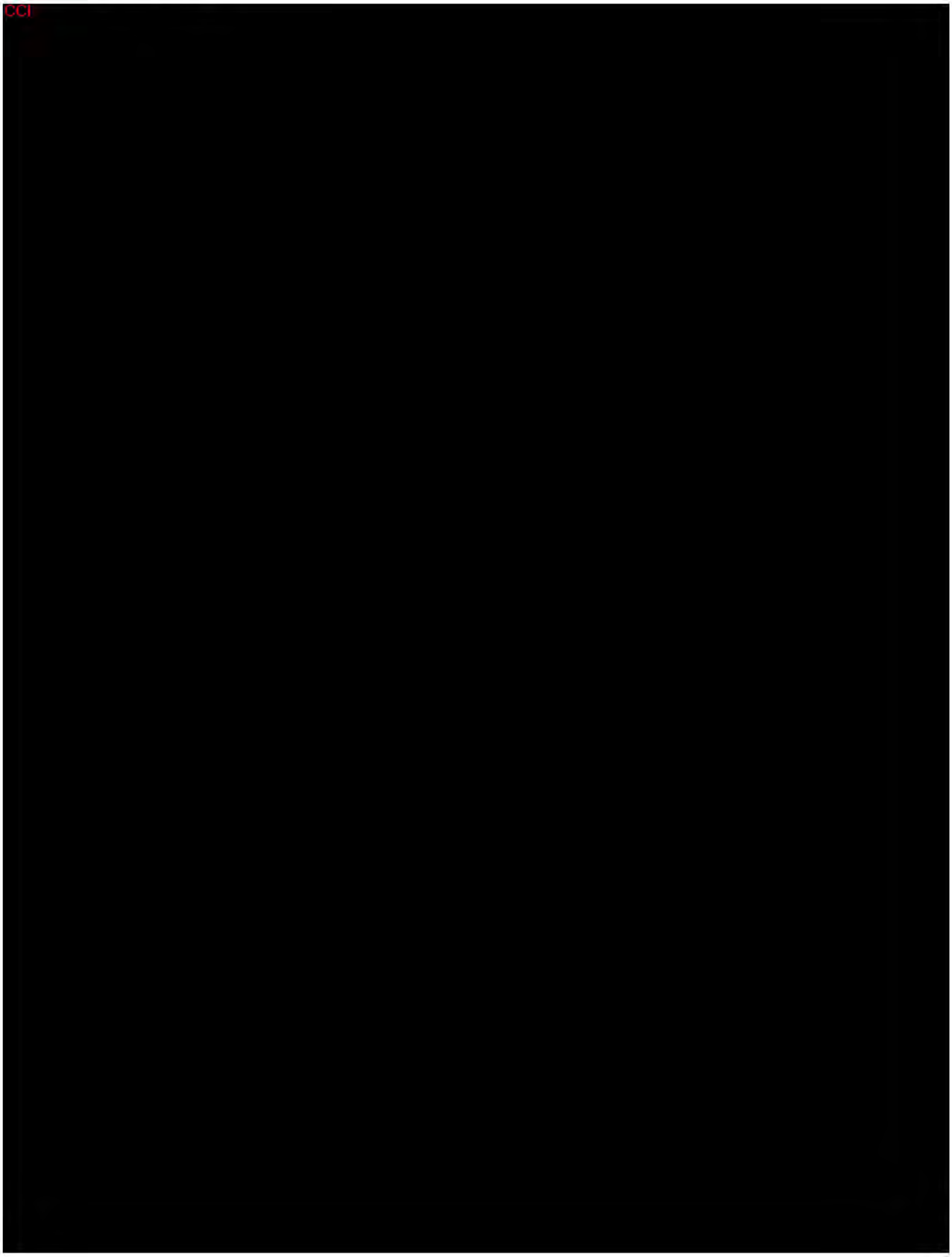

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[redacted]

9.8.2 Overall Survival

CCI

[redacted]

CCI

[redacted]

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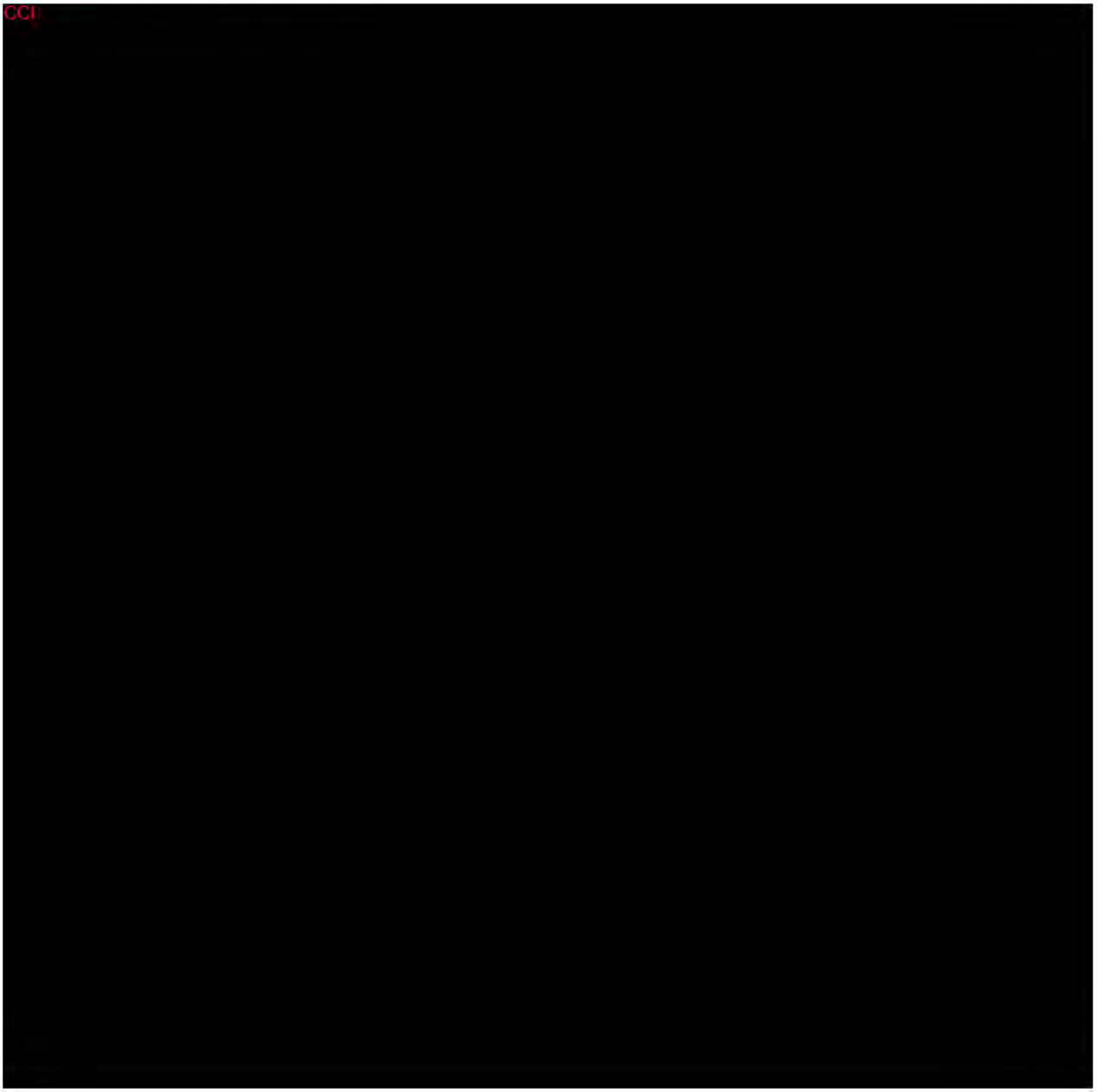

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[redacted]

CCI

[redacted]

CCI

[redacted]

9.9 Sample Size and Power Calculations

NOTE: As of Amendment 04, all the prespecified interim analyses after IA1 and final analysis of the study described in the SAP will not be performed. This section is retained for reference.

The sample size is estimated based on the primary endpoints of rPFS.

A total of approximately 1232 participants will be randomized in a 1:1 ratio to the pembrolizumab plus enzalutamide plus ADT group and the placebo plus enzalutamide plus ADT group, (approximately 616 participants per group) respectively.

CCI

[redacted]

[redacted]

[redacted] With [redacted] events, this study has approximately [redacted] power to demonstrate males treated with pembrolizumab + enzalutamide plus ADT have a longer median [redacted] than males treated with enzalutamide plus ADT at a [redacted] if the underlying constant [redacted] These calculations are based on the following assumptions: (1) a hazard ratio of [redacted] where [redacted] follows an [redacted] in the pembrolizumab + enzalutamide plus ADT group and a [redacted] in the enzalutamide plus ADT group; (2) interim analyses for efficacy evaluation as outlined in Section 9.7; and (3) an approximately [redacted].

[redacted] expected. [redacted] to demonstrate males treated with pembrolizumab + enzalutamide plus ADT have a longer [redacted] than males treated with enzalutamide plus ADT at a [redacted] [redacted]. These calculations are based on the following assumptions: (1) [redacted] in the pembrolizumab + enzalutamide plus ADT group and a median of [redacted] in the enzalutamide plus ADT group; (2) interim analyses for efficacy evaluation as outlined in Section 9.7; and (3) an approximately [redacted]

The [redacted] to demonstrate males treated with pembrolizumab + enzalutamide plus ADT have a [redacted] than males treated with enzalutamide plus ADT [redacted] These calculations are based on the following assumptions: (1) [redacted] in the enzalutamide plus ADT group; (2) interim analyses for efficacy evaluation as outlined in Section 9.7; and (3) an approximately [redacted].

The sample size and power calculations for rPFS, OS, TFST, and TTSSRE were performed in the [redacted]

Extension Portion in China:

To evaluate the consistency of efficacy and safety in the population in China compared with the global population, after completion of global portion enrollment, participants in China will continue to be randomized in a 1:1 ratio into the pembrolizumab plus enzalutamide plus ADT arm and placebo plus enzalutamide plus ADT arm until the planned sample size of approximately 186 participants in China is reached. Participants in China randomized after completion of enrollment in the global portion will not be included in the analysis of the global portion.

9.10 Subgroup Analyses

To determine whether the treatment effect is consistent across various subgroups, the estimate of the between-group treatment effect (with a nominal 95% CI) for the primary endpoints will be estimated and plotted within each category of the following classification variables:

CCI

In addition, a Forest plot will be produced, which provides the estimated point estimates and confidence intervals for the treatment effect across the categories of subgroups listed above.

In the event that there are a small number of responses/events in one or more strata, for the purpose of analysis strata will be combined to ensure sufficient number of responses/events in each stratum. Details regarding the combining of strata will be specified in the sSAP prior to database lock based on a blinded review of response counts by stratum.

Country-specific or region-specific populations may also be analyzed per local regulatory requirement.

9.11 Compliance (Medication Adherence)

Drug accountability data for study intervention will be collected during the study. Any deviation from protocol-directed administration will be reported.

9.12 Extent of Exposure

The extent of exposure for enzalutamide will be summarized as duration of treatment in days. The extent of exposure for pembrolizumab/placebo will be summarized as duration of treatment in cycles. Dose interruption for each drug, dose reduction or dose increase for

enzalutamide will be summarized. Summary statistics will be provided on Extent of Exposure for the APaT population.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Code of Conduct for Interventional Clinical Trials

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD)

I. Introduction

A. Purpose

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD), through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, planning, conducting, analyzing, and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with MSD's global standards, local and/or national regulations (including all applicable data protection laws and regulations), and International Council for Harmonisation Good Clinical Practice (ICH GCP) E6 and ICH General Considerations for Clinical Studies E8, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Highest ethical and scientific standards shall be endorsed for all clinical interventional investigations sponsored by MSD irrespective of the party (parties) employed for their execution (e.g., contract research organizations, collaborative research efforts). This Code is not intended to apply to trials that are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials, which are not under the full control of MSD.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy, and/or pharmacokinetic or pharmacodynamic indices of MSD or comparator products. Alternatively, MSD may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine patient preferences, etc.

The design (i.e., participant population, duration, statistical power) must be adequate to address the specific purpose of the trial and shall respect the data protection rights of all participants, trial site staff and, where applicable, third parties. Input may be considered from a broad range of stakeholders, including patient advocacy groups/patients representing the trial population, caregivers, and healthcare providers to ensure operational feasibility. Trial design also includes

proactive identification of critical to quality factors utilizing a risk-based approach. Plans are then developed to assess and mitigate risks to those factors as appropriate during the trial. All trial protocols are and will be assessed for the need and capability to enroll underrepresented groups. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

MSD's clinical trials are conducted globally in many different countries and in diverse populations, including people of varying age, race, ethnicity, gender, and accounting for other potential disease related factors. MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel (or individuals acting on behalf of MSD) to assess the ability to successfully conduct the trial. Individuals involved in trial conduct receive training commensurate with their role prior to their becoming involved in the trial.

Where appropriate, and in accordance with regulatory authority guidance, MSD will make concerted efforts to raise awareness of clinical trial opportunities in various communities. MSD will seek to engage underrepresented groups and those disproportionately impacted by the disease under study. MSD will support clinical trial investigators to enroll underrepresented groups and expand access to those who will ultimately use the products under investigation.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if potential fraud, scientific/research misconduct, privacy incidents/breaches or Clinical Trial-related Significant Quality Issues are reported, such matters are investigated. When necessary, appropriate corrective and/or preventative actions are defined and regulatory authorities and/or ethics review committees are notified.

B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish the primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the pre-specified plans for data analysis. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses it conducts that are important to patients, physicians, and payers. Some early phase or pilot trials are intended to be hypothesis generating rather than hypothesis testing; in such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues such as multiplicity.

MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. MSD funding of a trial will be acknowledged in publications.

III. Participant Protection

A. Regulatory Authority and Ethics Committee Review (Institutional Review Board [IRB]/Independent Ethics Committee [IEC])

All protocols and protocol amendments will be submitted by MSD for regulatory authority acceptance/authorization prior to implementation of the trial or amendment, in compliance with local and/or national regulations.

The protocol, protocol amendment(s), informed consent form, investigator's brochure, and other relevant trial documents must be reviewed and approved by an IRB/IEC before being implemented at each site, in compliance with local and/or national regulations and ICH Guidelines. Changes to the protocol that are required urgently to eliminate an immediate hazard and to protect participant safety may be enacted in anticipation of ethics committee approval. MSD will inform regulatory authorities of such new measures to protect participant safety, in compliance with local and/or national regulations.

B. Safety

The guiding principle in decision-making in clinical trials is that participant welfare is of primary importance. Potential participants will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care.

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Trial designs include procedures and systems for the identification, monitoring, and reporting of safety concerns. Participants may withdraw from an MSD trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

During trial planning, the need for an independent Data Monitoring Committee (DMC) is assessed. DMC review of data accumulated during the conduct of the trial is integral to the well-being of trial participants.

C. Confidentiality

MSD is committed to safeguarding participant confidentiality, to the greatest extent possible, as well as all applicable data protection rights. Unless required by law, only the investigator, Sponsor (or individuals acting on behalf of MSD), ethics committee, and/or regulatory authorities will have access to confidential medical records that might identify the participant by name.

D. Genomic Research

Genomic research will only be conducted in accordance with a protocol and informed consent authorized by an ethics committee.

E. Trial Results

At the time of providing informed consent and in accordance with local laws and regulations, participants should be informed about the plans for availability of trial results.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is MSD's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of MSD trials. MSD does not pay incentives to enroll participants in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

MSD does not pay for participant referrals. However, MSD may compensate referring physicians for time spent on medical record review and medical evaluation to identify potentially eligible participants.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by MSD, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local ethics committee may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, all publications resulting from MSD trials will indicate MSD as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc) will be consistent with local guidelines and practices.

V. Investigator Commitment

Investigators will be expected to review MSD's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

10.1.2 Financial Disclosure

Financial disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for

financial disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, frequently known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.1.3 Data Protection

The Sponsor will conduct this study in compliance with all applicable data protection regulations.

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.3.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the IRB, IEC, or similar or expert committee, affiliated institution, and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution, and employees. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.3.2 Confidentiality of Participant Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/IEC, or regulatory authority representatives may consult and/or copy study documents to verify worksheet/CRF data. By signing the consent form, the participant agrees to this process. If study documents will be photocopied during the process of verifying worksheet/CRF information, the participant will be identified by unique code only; full names/initials will be masked before transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all participant data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules, and regulations.

10.1.3.3 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this study. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.1.4 Committees Structure

10.1.4.1 External Data Monitoring Committee

To supplement the routine study monitoring outlined in this protocol, an external DMC will monitor the interim data from this study. The voting members of the committee are external to the Sponsor. The members of the DMC must not be involved with the study in any other way (eg, they cannot be study investigators) and must have no competing interests that could affect their roles with respect to the study.

The DMC will make recommendations to the EOC regarding steps to ensure both participant safety and the continued ethical integrity of the study. Also, the DMC will review interim study results, consider the overall risk and benefit to study participants (Section 9.7 Interim Analysis) and recommend to the EOC whether the study should continue in accordance with the protocol.

Specific details regarding composition, responsibilities, and governance, including the roles and responsibilities of the various members and the Sponsor protocol team; meeting facilitation; the study governance structure; and requirements for and proper documentation of DMC reports, minutes, and recommendations will be described in the DMC charter that is reviewed and approved by all the DMC members.

10.1.5 Publication Policy

The results of this study may be published or presented at scientific meetings. The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

If publication activity is not directed by the Sponsor, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

Authorship will be determined by mutual agreement and in line with ICMJE authorship requirements.

10.1.6 Compliance with Study Registration and Results Posting Requirements

Under the terms of the FDAAA of 2007 and the EMA clinical trial Directive 2001/20/EC, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu, or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trials directive mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study-site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials directive, or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this study or its results to those registries.

10.1.7 Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol, generally accepted standards of GCP (eg, ICH GCP: Consolidated Guideline and other generally accepted standards of GCP), and all applicable federal, state, and local laws, rules, and regulations relating to the conduct of the clinical study.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by MSD, is provided in this appendix under the Code of Conduct for Clinical Trials.

The investigator agrees not to seek reimbursement from participants, their insurance providers, or from government programs for procedures included as part of the study reimbursed to the investigator by the Sponsor.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this study.

The investigator agrees to provide the Sponsor with relevant information from inspection observations/findings to allow the Sponsor to assist in responding to any citations resulting from regulatory authority inspection and will provide the Sponsor with a copy of the proposed response for consultation before submission to the regulatory authority.

Persons debarred from conducting or working on clinical studies by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's studies. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

For investigators located in countries with serious breach reporting requirements, investigator will promptly report to the Sponsor any serious breach or suspected serious breach that occurs in compliance with those requirements. Unless more specifically defined in the applicable requirements, a serious breach is any breach of the applicable clinical trial regulation or of the clinical trial protocol which is likely to affect to a significant degree: (i) the safety or rights of a trial participant, or (ii) the reliability and robustness of the data generated in the clinical trial.

10.1.8 Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator or qualified designee is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the study site upon request for inspection, copying, review, and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor or any regulatory authorities as a result of an audit or inspection to cure deficiencies in the study documentation and worksheets/CRFs.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data review and verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including participants' documented informed consent, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.9 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. The investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's participants. Source documents and data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator/institution may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.10 Study and Site Closure

The Sponsor or its designee may stop the study or study-site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

In the event the Sponsor prematurely terminates a particular study site, the Sponsor or designee will promptly notify that study site's IRB/IEC as specified by applicable regulatory requirement(s).

10.2 Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 20 will be performed by the central laboratory.

Results of predose laboratory procedures must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of pembrolizumab/placebo. After randomization, local laboratory results are permitted in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is used, it is important that the sample for central analysis is obtained in parallel. Additionally, if the use of local laboratory test results in a change in study participant management, or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.1 and Section 5.2 of the protocol, respectively.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

PD-L1 and PSA results are not reported back to sites to prevent early withdrawal of participants from study intervention.

Table 20 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH Reticulocytes	WBC count with Differential: Absolute Neutrophil Count (ANC) Lymphocytes Monocytes Eosinophils Basophils	
Chemistry	Blood Urea Nitrogen (BUN)	Potassium	Aspartate Aminotransferase (AST)/Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total bilirubin (and direct bilirubin, if total bilirubin is elevated above the upper limit of normal)
	Albumin	Bicarbonate	Chloride	Phosphorous
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose (nonfasting)	Calcium	Alkaline phosphatase	
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase • Microscopic examination (if blood or protein is abnormal)			
Other Tests	• Testosterone (not required to be reviewed predose) • Thyroid function tests • PT or INR and PTT/aPTT			

ALT alanine aminotransferase; ANC absolute neutrophil count; aPTT activated partial thromboplastin time; AST aspartate aminotransferase; BUN blood urea nitrogen; INR international normalized ratio; MCH mean corpuscular hemoglobin; MCV mean corpuscular volume; PT prothrombin time; PTT partial thromboplastin time; RBC red blood cell; SGOT serum glutamic oxaloacetic transaminase; SGPT serum glutamic pyruvic transaminase; WBC white blood cell.

The investigator (or medically qualified designee) must document their review of each laboratory safety report.

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definitions of Medication Error, Misuse, and Abuse

Medication Error

This is an unintended failure in the drug treatment process that leads to or has the potential to lead to harm to the patient.

Misuse

This refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the terms of the product information.

Abuse

This corresponds to the persistent or sporadic intentional, excessive use of a medicinal product for a perceived psychological or physiological reward or desired nontherapeutic effect.

10.3.2 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.
- Note: For purposes of AE definition, study intervention includes any pharmaceutical product, biological product, vaccine, diagnostic agent, medical device, combination product, or protocol-specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), manufactured by, licensed by, provided by, or distributed by the Sponsor for human use in this study.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.

- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgical procedure(s) planned prior to informed consent to treat a preexisting condition that has not worsened.
- Refer to Section 8.4.6 for protocol-specific exceptions.

10.3.3 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death
b. Is life-threatening
   - The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization
   - Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a preexisting condition that has not worsened is not an SAE.) A preexisting condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the participant's medical history.

d. Results in persistent or significant disability/incapacity
   - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
   - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect
   - In offspring of participant taking the product regardless of time to diagnosis.

f. Other important medical events
   - Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.
   - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.4 Additional Events Reported

Additional events that require reporting

In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor.

- Is a new cancer (that is not the cancer under study) as noted in Section 8.4.1.
- Is associated with an overdose.

10.3.5 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.

- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity/toxicity

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.
- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) according to the NCI CTCAE, version 5.0. Any AE that changes CTCAE grade over the course of a given episode will have each change of grade recorded on the AE CRFs/worksheets.
  - Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
  - Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
  - Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
  - Grade 4: Life-threatening consequences; urgent intervention indicated.
  - Grade 5: Death related to AE.

Assessment of causality

- Did the study intervention cause the AE?
- The determination of the likelihood that the study intervention caused the AE will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the AE based upon the available information.

- **The following components are to be used to assess the relationship between the study intervention and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the study intervention caused the AE:**
  - **Exposure:** Is there evidence that the participant was actually exposed to the study intervention such as: reliable history, acceptable compliance assessment (pill count, diary, etc), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
  - **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the study intervention? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with IMP)?
  - **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors.
  - **Dechallenge:** Was the study intervention discontinued or dose/exposure/frequency reduced?
    - If yes, did the AE resolve or improve?
    - If yes, this is a positive dechallenge.
    - If no, this is a negative dechallenge.

    (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the study intervention; (3) the study is a single-dose drug study; or (4) study intervention (s) is/are only used 1 time.)
  - **Rechallenge:** Was the participant reexposed to the study intervention in this study?
    - If yes, did the AE recur or worsen?
    - If yes, this is a positive rechallenge.
    - If no, this is a negative rechallenge.

    (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability; (2) the study is a single-dose drug study; or (3) study intervention (s) is/are used only 1 time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE THAT WAS SERIOUS AND MAY HAVE BEEN CAUSED BY THE STUDY INTERVENTION, OR IF REEXPOSURE TO THE STUDY INTERVENTION POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL, AND IF REQUIRED, THE IRB/IEC.

- **Consistency with study intervention profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the study intervention or drug class pharmacology or toxicology?

- The assessment of relationship will be reported on the case report forms/worksheets by an investigator who is a qualified physician according to their best clinical judgment, including consideration of the above elements.
- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a study intervention relationship).
  - Yes, there is a reasonable possibility of study intervention relationship:
    - There is evidence of exposure to the study intervention. The temporal sequence of the AE onset relative to the administration of the study intervention is reasonable. The AE is more likely explained by the study intervention than by another cause.
  - No, there is not a reasonable possibility of study intervention relationship:
    - Participant did not receive the study intervention OR temporal sequence of the AE onset relative to administration of the study intervention is not reasonable OR the AE is more likely explained by another cause than the study intervention. (Also entered for a participant with overdose without an associated AE.)
- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.
- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.
- For studies in which multiple agents are administered as part of a combination regimen, the investigator may attribute each AE causality to the combination regimen or to a single agent of the combination. In general, causality attribution should be assigned to the combination regimen (ie, to all agents in the regimen). However, causality attribution may be assigned to a single agent if in the investigator's opinion, there is sufficient data to support full attribution of the AE to the single agent.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the CRF.
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.6 Reporting of AEs, SAEs, and Other Reportable Safety Events to the Sponsor

AE, SAE, and other reportable safety event reporting to Sponsor via electronic data collection tool

- The primary mechanism for reporting to the Sponsor will be the EDC tool.
  - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
  - If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
  - Reference Section 8.4.1 for reporting time requirements.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).
- Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

SAE reporting to the Sponsor via paper CRF

- If the EDC tool is not operational, facsimile transmission or secure email of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Study File Binder (or equivalent).

10.4 Appendix 4: Medical Device and Drug–Device Combination Products: Product Quality Complaints/Malfunctions: Definitions, Recording, and Follow-up

Not applicable.

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below):

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy
    For individuals with permanent infertility due to an alternate medical cause other than the above (eg, Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

    Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2 Contraceptive Requirements

Male participants are eligible to participate if they agree to the following during the intervention period and for at least 120 days after the last dose of study intervention:

- Refrain from donating sperm

  PLUS either:

- Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent

  OR

- Must agree to use contraception, unless confirmed to be azoospermic (vasectomized or secondary to medical cause [Appendix 5]), as detailed below:

  - Agree to use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a woman of childbearing potential (WOCBP) who is not currently pregnant. Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile-vaginal penetration.

Male participants must agree to use male condom when engaging in any activity that allows for passage of ejaculate to another person of any sex.

10.6 Appendix 6: Collection and Management of Specimens for Future Biomedical Research

Not applicable.

10.7 Appendix 7: Country-specific Requirements

10.7.1 Laboratory Testing

HIV Status

While the protocol does not require specific testing for HIV at Screening, it does require testing if required by the local health authority. Sites should check with their local health authority to inquire if country-specific guidance regarding mandatory HIV testing at Screening is required. This can also be performed per the discretion of the investigator, if desired. Perform locally if required.

Hepatitis B/C Status

While the protocol does not require specific testing for hepatitis B/C at Screening, it does require testing if required by the local health authority. Sites should check with their local health authority to inquire if country-specific guidance regarding mandatory hepatitis B/C testing at Screening is required. This can also be performed per the discretion of the investigator, if desired. Perform locally if required.

10.7.2 Country-specific Information

CCI

10.8 Appendix 8: Description of the Prostate Cancer Working Group (PCWG) Process for Assessment of Bone Lesions

The rules for evaluation of response and progression based on bone lesions were created by the PCWG and published as part of PCWG3 [Scher, H. I., et al 2016]. All bone lesions are evaluated according to these rules, including assessment at screening/baseline and evaluation of response.

10.8.1 Imaging Methods

The PCWG rules were designed based on the radionuclide (Tc-99m) bone scintigraphy. Other modalities, including FDG-PET, sodium fluoride PET, bone MRI, etc. may have individual advantages, but the PCWG rules were not created with the performance characteristics of these methods in mind and should not be used instead of radionuclide bone scan.

Only bone lesions seen by bone scan may be followed for assessment of tumor treatment response. Bone disease seen by CT only (not visible on bone scan) is presumed not to represent active disease and should not be documented as a bone lesion (sclerotic lesions seen on CT may represent healed disease or non-malignant confounders such as bone infarcts or other benign findings).

10.8.2 Documentation of Bone Lesions at Baseline

At baseline, individual bone lesions may be recorded as non-target lesions only, and the number of bone lesions should be noted.

10.8.3 Assessment of Bone Response at Subsequent Imaging Time Points

At all follow-up timepoints, bone disease will be classified as PD (progressive disease), PDu (progressive disease unconfirmed), Non-PD (no progressive disease), NED (no evidence of disease), or NE (non-evaluable). The definitions are summarized in the following table and described in more detail below.

Bone Response	Definition
PD	**Progressive disease:** 2 new lesions, not flare, persistent
PDu	**Progressive disease unconfirmed:** Temporary marker of possible PD, to be updated to PD or non-PD once a subsequent scan is available. If this is the final visit, the visit response will remain PDu
Non-PD	**Non-progressive disease:** At least one bone lesion present, but not enough to trigger PD
NE	**Non-evaluable:** Status of bone lesions cannot be determined (scan quality, scan missing, etc.)
NED	**No evidence of disease:** No lesions seen on bone scan

10.8.4 Descriptions of Bone Response Categories

10.8.4.1 No Evidence of Disease

No lesions seen on bone scan at this visit. Either none were seen at baseline, or all completely resolved on subsequent imaging.

10.8.4.2 Non-progression (Non-PD)

At least one bone lesion is present on the scan at this visit, but the conditions for progression have not been met, because there are not at least two new lesions present.

10.8.4.3 Unconfirmed Progressive Disease (PDu)

At least two new bone lesions are present, but an additional scan is required for confirmation. This response category is meant as a placeholder that reflects temporary uncertainty and is updated to PD or non-PD once a subsequent bone scan is available.

10.8.4.4 Progressive Disease (PD)

At least two new bone lesions are present, which have been confirmed to not represent flare or any other confounder (see below), and which are persistent for at least 6 weeks. The new bone lesions do not all have to appear at the same time. Thus, if one new lesion appears at visit N, and another new lesion at visit N+1, visit N+1 is considered to represent progressive disease.

10.8.4.5 Confirmation of Progression

Radiographic progression of bone lesions is defined as the appearance of ≥2 new bone lesions on radionuclide bone scan. When ≥2 new bone lesions are first observed, this is classified as PDu, which marks the possibility of progression that will be resolved by the next scan.

10.8.4.5.1 For New Lesions Within the Flare Window (<12 weeks)

After a scan classified as PDu within the first 12 weeks of treatment, if the next bone scan outside the flare window shows at least two additional new bone lesions (in addition to the new lesions seen on the prior scan), the initial progression is considered confirmed, and the bone scan response updated to PD. Because this requires at least 2 new lesions, followed by another 2 new lesions, this is known as the "2+2 rule".

If the next bone scan outside the flare window does not show at least two additional new bone lesions, the lesions seen on the prior scan within the flare window are considered to be pre-existing lesions that became more visible because of the tumor flare phenomenon.

- The bone response at the prior visit is updated to non-PD
- The bone lesions seen within the flare window are ignored for the purposes of counting new lesions at later timepoints, since they were not new. This may be referred to as "re-baselining".

10.8.4.5.2 For New Lesions Outside the Flare Window (>12 weeks)

After a scan classified as PDu after the first 12 weeks of treatment, if at least 2 of the new lesions seen on that scan persist on the next bone scan performed at least 6 weeks later, this confirms the initial progression. The prior response is then updated to PD. If the new lesions have disappeared on this later scan, the prior response is updated to non-PD because these lesions are presumed to be non-malignant in nature. No re-baselining of lesions will occur in this scenario.

10.8.4.6 Superscan

A "superscan" occurs when there is diffuse skeletal involvement by tumor, such that individual bone lesions are not distinguishable. The bone scan may initially appear normal, because the increase bone uptake may be uniform, but can be distinguished by the faint or absent activity in the kidneys and urinary tract.

If there is a true superscan at baseline, identifying individual new bone lesions, and determining progression based on bone lesions, may be impossible.

If a superscan occurs after baseline, the patient's bone response will be recorded as PD. No subsequent imaging will be required for confirmation, because a superscan is extremely unlikely to be caused by benign conditions or tumor flare.

10.8.4.7 Management Following Confirmed PD

If repeat imaging does confirm PD, participants will be discontinued from study intervention.

Note: If a participant has confirmed radiographic progression as defined above, but the participant is achieving a clinically meaningful benefit, an exception to continue study intervention may be considered following consultation with the Sponsor. In this case, if study intervention is continued, tumor imaging should continue (reference the efficacy section of the protocol).

10.9 Appendix 9: Description of the iRECIST Process for Assessment of Disease Progression

Not applicable.

10.10 Appendix 10: Abbreviations

Abbreviation	Expanded Term
ADL	activities of daily living
ADT	androgen deprivation therapy
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
APaT	All-Participants-as-Treated
AST	aspartate aminotransferase
BCG	Bacillus Calmette Guérin
BICR	blinded independent central review
BPI-SF	Brief Pain Inventory Short Form
CD28	cluster of differentiation 28
CD3ζ	cluster of differentiation 3 zeta
CFR	Code of Federal Regulations
cHL	classical Hodgkin Lymphoma
CI	confidence interval
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CR	complete response
CrCl	Creatinine clearance
CRF	case report form
CRPC	castration-resistant prostate cancer
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor deoxyribonucleic acid
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
DCR	disease control rate
DOR	duration of response

Abbreviation	Expanded Term
DNA	deoxyribonucleic acid
EBRT	external-beam radiation therapy
ECG	electrocardiogram
ECI	event of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data collection
eDMC	external Data Monitoring Committee
ELISA	enzyme-linked immunoassay
EMA	European Medicines Agency
EOC	executive oversight committee
ESMO	European Society for Medical Oncology
EWB	emotional well-being
FACT-G	Functional Assessment of Cancer Therapy-General
FACT-P	Functional Assessment of Cancer Therapy-Prostate
FAPSI6	FACT Advanced Prostate Symptom Index 6
FAS	full analysis set
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FDG-PET	flurodeoxyglucose-positron emission tomography
FFPE	formalin-fixed, paraffin embedded
FSH	follicle stimulating hormone
FT3	free triiodothyronine
FT4	free thyroxine
FWB	functional well-being
GCP	Good Clinical Practice
GFR	glomerular filtration rate
H	Hypothesis
HCC	hepatic cell carcinoma
HCV	Hepatitis C virus

Abbreviation	Expanded Term
HGRAC	Human Genetic Resources Administration of China
HIV	human immunodeficiency virus
HNSCC	head and neck squamous cell carcinoma
HR	hazard ratio
HRQoL	health-related quality of life
HRT	hormone replacement therapy
IA	interim analysis
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
iCRO	Imaging Contract Research Organization
IEC	Independent Ethics Committee
Ig	immunoglobulin
IHC	immunohistochemistry
IL	interleukin
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
irAE	immune-related adverse event
IRB	Institutional Review Board
IRT	interactive response technology
ITT	Intent-to-Treat
IV	intravenous
IVD	in vitro diagnostic
KN	KEYNOTE
LHRH	luteinizing-hormone releasing hormone
mAb	monoclonal antibody
mCRPC	metastatic castration-resistant prostate cancer
mHSPC	metastatic hormone-sensitive prostate cancer
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid

Abbreviation	Expanded Term
MSI	microsatellite instability
N	number
NA	Not Applicable
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NE	non-evaluable
NED	no evidence of disease
NHA	next generation hormonal agents
NIMP	Non-Investigational Medicinal Product
Non-PD	non-progression
NSAID	non-steroidal anti-inflammatory drug
NSCLC	non-small cell lung cancer
ORR	objective response rate
OR	objective response
OS	overall survival
OTC	over-the-counter
PBPK	physiologically-based pharmacokinetic
PCS	Prostate Cancer Symptoms
PCWG	Prostate Cancer Working Group
PD	progressive disease
PD-1	programmed cell death 1
PD-L1	programmed cell death ligand 1
PD-L2	programmed cell death ligand 2
PDLC	predefined limit of change
PDu	unconfirmed progressive disease
PFS	progression-free survival
PFS2	Time from randomization to disease progression as determined by investigator assessment after next-line of therapy or death from any cause, whichever occurs first.
PIN	personal identification number
PK	pharmacokinetic

Abbreviation	Expanded Term
PKCθ	protein kinase C-theta
PMBCL	primary mediastinal B-cell lymphoma
PO	Per oral (by mouth)
PR	partial response
PRES	posterior reversible encephalopathy syndrome
PRO	patient-reported outcome
PSA	prostate-specific antigen
PSMA-PET	Prostate Specific Membrane Antigen-Positron Emission Tomography
PT	prothrombin time
PTT	partial thromboplastin time
PWB	physical well-being
Q2W	every 2 weeks
Q3W	every 3 weeks
QD	every day
RECIST 1.1	Response Evaluation Criteria in Solid Tumors Version 1.1
RMST	restricted mean survival time
RNA	ribonucleic acid
rPFS	radiographic progression-free survival
RPSFT	rank preserving structural failure time
SAE	serious adverse event
SCF	Sponsor Communication Form
SD	stable disease
SIM	Site Imaging Manual
SLAB	supplemental laboratory
SNP	single nucleotide polymorphism
SoA	schedule of activities
SOC	standard of care
SPECT	Single Photon Emission Computer Tomography
sSAP	supplemental Statistical Analysis Plan
SSRE	symptomatic skeletal-related event

Abbreviation	Expanded Term
SUSAR	suspected unexpected serious adverse reaction
SWB	social/family well-being
T3	total triiodothyronine
TEA	Treatment Eligibility Assessment
TFST	time to initiation of the first subsequent anticancer therapy
TMDD	target-mediated drug disposition
TOI	Trial Outcome Index
TRAE	treatment-related adverse event
TTBP	time to bone progression
TTPP	time to pain progression
TTSSRE	time to symptomatic skeletal-related event
UC	urothelial carcinoma
ULN	upper limit of normal
US	United States
VAS	visual analog scale
WOCBP	woman/women of childbearing potential
ZAP70	zeta-chain-associated protein kinase

10.11 Appendix 11: Eastern Cooperative Oncology Group Performance Status

Grade	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50 of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50 of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead
Source: [Oken, M. M., et al 1982]	

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